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Evolving Diagnostic Role of Cardiac Magnetic Resonance in Acute Coronary Syndrome

Dr Amardeep Ghosh Dastidar

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Health Sciences.

School of Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences, July 2019.

Word count: 35024

Abstract

Acute coronary syndrome (ACS) encompasses a spectrum of clinical conditions associated with reduced blood supply to the myocardium. In UK and other developed countries, although the incidence is decreasing but it is still the leading cause of premature death worldwide.(1) Over the last three decades, cardiac magnetic resonance imaging (CMR) has emerged as a promising non-invasive modality in the assessment of patients with suspected and established ACS due to its good spatial resolution, high reproducibility, and myocardial tissue characterization capabilities, thereby aiding in the diagnosis, guiding clinical decision-making, and improving risk stratification.

In this thesis we primarily looked at 2 cohort of patients **A) Myocardial infarction with non-obstructed coronaries(MINOCA)** group (388 subjects) and **B) ST segment elevation myocardial infarction (STEMI)** cohort (30 subjects) treated with primary percutaneous coronary intervention. The findings of the acute revascularised STEMI was compared with 20 healthy volunteers and 30 subjects with previous myocardial infarction. All participants underwent CMR in a 1.5T Avanto, Siemens Scanner.

MINOCA study - In a large cohort of MINOCA, CMR (median 37days from presentation) established a diagnosis in almost 3/4 of cases, the most common diagnoses being myocarditis and MI, followed by cardiomyopathy.

The study demonstrated that the diagnostic value of CMR is improved significantly when carried out within 2 weeks from presentation.

CMR made a significant additive clinical impact on management and/or diagnosis in 66% of patients, with LGE being the best independent predictor of impact. Moreover, the clinical impact of CMR improved significantly when carried out within 2 weeks from presentation.

The MINOCA study also demonstrated that among the conventional risk factors and CMR characteristics, ST-segment elevation on presentation ECG and CMR diagnosis of cardiomyopathy were independent predictors of mortality in MINOCA. Combined analysis of CMR diagnosis and ECG at presentation may allow robust stratification of patient outcomes.

In STEMI – Via non-invasive advanced CMR relaxometry technique the study demonstrated that in STEMI the remote myocardium is also affected when compared to normal healthy myocardium. The native T1 in remote myocardium is an independent associate of MVO.

In a further study it was demonstrated that native T1 mapping correlates significantly with transmural extent of infarct (TEI) thereby differentiating between normal, infarcted viable, and infarcted non-viable myocardium with distinctive T1 profiles in both chronic and acute MI. Native T1 mapping performed better in chronic MI compared to acute due to the absence of myocardial oedema and microvascular obstruction. T1 mapping holds promise for viability assessment without the need for gadolinium contrast agents.

Dedication

This dissertation is dedicated to my loving wife, Dr Sumana Chatterjee and my son Master Aaron Ghosh Dastidar. Your love, support and confidence in me have enabled me to overcome all the challenges. I would also like to thank my sister in law Ms Sulagna Chatterjee for supporting me during my research fellowship. Without their help I would never have been able to complete my project.

I also dedicate this dissertation to my parents Mr Arup Ghosh Dastidar and Mamata Ghosh Dastidar, my elder brothers Mr Anindya Ghosh Dastidar and Mr Amit Ghosh Dastidar. Without their care, guidance, motivation and inspiration, I would not be where I am today.

Acknowledgements

I am ever grateful to my principal supervisor **Dr Chiara Bucciarelli-Ducci**. Thank you for all your support, guidance, mentorship and above all believing in me. You taught me all the essential requirements to be a true clinical academic. You were really an Avatar in my life who brought the turning point in my career. My sincere gratitude to you for being such an amazing, inspiring mentor and ever helpful friend.

I would like to thank my co supervisor **Prof Andreas Baumbach**. Thank you for all your help and support. I would also like to acknowledge the help and support that I received from my other supervisors - **Dr Tom Johnson, Dr Angus Nightingale, Prof Gianni Angelini, Dr Julian Strange, Dr Stephen Dorman, Dr Mark Hamilton and Dr Nathan Manghat**.

To my research fellow colleague **Dr Jonathan Rodrigues**, thank you for being such a fantastic friend and colleague. Your company made the research fellowship years so memorable and enjoyable. Miss those afternoon lunch sessions at Level 9 BRI exchanging research ideas, sharing weekend tales, and general chit-chats.

I would also like to thank all my co-research fellow and statistician friends - **Dr Estefania DeGarate, Dr Anna Baritussio, Dr Alessandra Scatteia, Dr Guilia Pontecorboli, Dr Iwan Harries, Dr Sarah El Gamal, Dr Elisa McAlindon, Dr Elena Milano, Dr Stephen Lyen, Dr Gergely Szantho, Dr Tamas Erdei, Mr Domenico Vito Bruno and Dr Giovanni Biglino**.

To **Mr Benny Lawton**, CMR radiographer superintendent, thank you for being such a brilliant colleague and friend. You are the true Magnet in the unit. You made those research years so enjoyable. I would also like to thank all the other CMR radiographers – you are an amazing bunch.

To all the eSSC medical students at University of Bristol whom I have supervised, thank you for all your hard work and dedication.

Author's declaration

I declare that the work in my dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views or opinions expressed in the dissertation are those of the author.

SIGNED: DATE:.....

Publications

Dr Amardeep Ghosh Dastidar was the first author writing the text for the following manuscripts which were accepted for publication during the course of this project, elements of which are comprised in this thesis and referenced accordingly:

- **Dastidar AG**, Baritussio A, De Garate E et al. Prognostic role of cardiac MRI and conventional risk factors in Myocardial Infarction with non-obstructed coronary arteries. **JACC Cardiovasc Imaging** 2019 Feb (epub ahead of print)
- **Dastidar AG**, Harries I, Pontecorboli G et al. Native T1 mapping to detect extent of acute and chronic myocardial infarction: comparison with late gadolinium enhancement technique. **Int J Cardiovasc Imaging** 2019 Mar;35(3):517-527
- **Dastidar AG**, Rodrigues JCL, Johnson T et al. Myocardial Infarction with non-obstructed coronary artery: Impact of CMR early after presentation. **JACC Cardiovasc Imaging** 2017 Oct;10:1204-1206
- **Dastidar AG**, Rodrigues JCL, Baritussio A et al. MRI in the assessment of ischaemic heart disease. **Heart** 2016

Feb;102(3):239-52

- **Dastidar AG, Rodrigues JCL, Ahmed N et al.** The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. **Curr Cardiovasc Imaging Rep.** 2015;8(8):28
- **Dastidar AG, Frontera A, Palazzuoli A, et al.** TakoTsubo cardiomyopathy: unravelling the malignant consequences of a benign disease with cardiac magnetic resonance. **Heart Fail Rev.** 2015 Jul;20(4):415-421.

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Abbreviations

ACS: Acute coronary syndrome

AF: Atrial fibrillation

AHA: American Heart Association

AUC: area under the curve

CAD: coronary artery disease

CE-SSFP: contrast-enhanced steady state free precession

CI: confidence interval

CMR: cardiovascular magnetic resonance

CoV: coefficient of variability

DCM: Dilated cardiomyopathy

ECM: extracellular matrix

ECV: extracellular volume fraction

EGE: early gadolinium enhancement

ESA: endocardial surface area

ESC: European Society of Cardiology

FB: free breathing

FPP: first pass perfusion

FWHM: full width half maximum

HCM: Hypertrophic cardiomyopathy

ICC: intra-class correlation coefficient

IMH: intramyocardial haemorrhage

IR: inversion recovery

IHD: ischaemic heart disease

LGE: late gadolinium enhancement

LV: left ventricle/ ventricular

LVEDV: left ventricular end-diastolic volume

LVEF: left ventricular ejection fraction

LVESV: left ventricular end-systolic volume

LVM: left ventricular mass

MACE: major adverse clinical outcome

MagIR: magnitude-reconstructed inversion recovery

MDC: minimal detectable change

MDC95: minimal detectable change with 95% confidence

MI: myocardial infarction/ infarct

MINOCA: myocardial infarction with non-obstructed coronary artery

MOCO: motion-corrected

MOLLI: Modified Look Locker Inversion recovery

MSI: myocardial salvage index

MVO: microvascular obstruction

NSTEMI: non-ST segment elevation myocardial infarction

PET: positron emission tomography

PPCI: primary percutaneous coronary intervention

PSIR: phase sensitive inversion recovery

RCT: randomised controlled trials

ROC: receiver operator characteristic

ROI: region of interest

SD: standard deviation

SEM: standard error of the mean

SPECT: single photon computed tomography

STEMI: ST-segment elevation myocardial infarction

STIR: short tau inversion recovery

TCM: Takotsubo cardiomyopathy

TEI: transmural extent of infarction

WIP: work in progress

1 Introduction

1.1 *Role of CMR in the Acute Coronary Syndrome*

Acute coronary syndrome (ACS) encompasses a spectrum of clinical conditions associated with reduced blood supply to the myocardium. In UK and other developed countries, although the incidence is decreasing but it is still the leading cause of premature death worldwide.(1) Over the last three decades, cardiac magnetic resonance imaging (CMR) has emerged as a promising non-invasive modality in the assessment of patients with suspected and established ACS due to its good spatial resolution, high reproducibility, and myocardial tissue characterization capabilities, thereby aiding in the diagnosis, guiding clinical decision-making, and improving risk stratification.

In the assessment of ACS, clinicians are often posed with the dilemma of which non-invasive cardiovascular imaging modality to choose. CMR is superior to several other functional imaging modalities, especially in certain circumstances like in obese subjects, in females, in acute myocardial injury and in the assessment of myocardial viability. (2,3)

The following sections provide an overview of why, when and where CMR may fit into the routine clinical practice in the assessment of patients with suspected and established ACS.

1.2 *CMR in clinical decision making- Acute Coronary Syndromes*

1.2.1 a) Non-ST elevation Acute Coronary Syndrome (NSTEMI-ACS)

The evidence for using CMR in NSTEMI-ACS is growing. The 2015 European Society of Cardiology (ESC) guidelines on the management of NSTEMI-ACS suggest CMR should be considered in few specific settings. (4,5) **Table 1-1.**

Table 1-1 Recent ESC guidelines: Indications for use of CMR in IHD (5–8)

In Non ST-Elevation – ACS (ESC Guideline 2015) (4,5)
In patients without recurrence of pain, normal ECG findings, negative troponins tests, and a low risk score, a non- invasive stress test for inducible ischaemia is recommended before deciding on an invasive strategy
CMR imaging is useful to assess myocardial viability and to detect myocarditis
In ST-Elevation Myocardial Infarction (ESC Guideline 2017) (6,8)
CMR may be used as an alternative for assessment of infarct size and resting LV function, if echocardiography is not feasible, after STEMI
For patients with multivessel disease, or in whom revascularization of other vessels is considered, stress imaging to demonstrate ischaemia and viability is an option

CMR has a role in detection of ACS in low risk patients presenting with chest pain, normal ECG, normal cardiac biomarkers and prior to deciding on an invasive strategy. The sensitivity and specificity of CMR for detecting subsequent ACS in patients presenting with cardiac chest pain without MI, is high (84% and 85%, respectively) (9). By adding an oedema imaging, the diagnostic accuracy increased further (upto 93%). (10) A normal stress CMR has a high negative predictive value in troponin-negative ACS. (11) In a NSTEMI study, stress CMR reliably predicted the significant coronary stenosis (sensitivity, 96%; specificity, 83%). Moreover, CMR assessment was superior to TIMI risk score (12).

In patients with multivessel disease (MVD), myocardial oedema imaging (T2-weighted sequence) can help in identifying the culprit vessel. (13)

However, the CMR studies on NSTEMI-ACS are small and single-centre. CMR at the emergency department is hardly used due to limited access, long scanning times and the cost. However, in our Institution it is sometime offered prior to angiogram, to assess myocardial viability (LGE imaging) and identify the culprit vessel (oedema imaging) to guide revascularization.

1.2.2 Myocardial infarction with non-obstructed coronary artery (MINOCA)

Globally, acute coronary syndrome (ACS) still remains one of the leading causes of mortality and morbidity. Emergency or early angiography is recommended in suspected ACS with ST-elevation Myocardial Infarction (STEMI) or in non-ST elevation ACS (NSTEMI-ACS) with an intermediate-high Global Registry of Acute Coronary Events (GRACE) score. The literature suggests that 7-10% of patients presenting with STEMI and 10-15% of patients presenting with NSTEMI-ACS have unobstructed coronary artery disease (CAD) on urgent angiography (14–21). Patients with ACS and unobstructed coronary arteries, termed MINOCA represent a clinical dilemma and their management is quite variable in current practice. Secondary prevention medications for ACS are used less frequently in these patients than in patients with obstructive CAD (22,23). This is partly due to our lack of understanding of the underlying patho-physiological mechanisms leading to the troponin rise and the lack of clear-cut guidelines. A common clinical misconception is that patients in this group have a relatively good prognosis in comparison with patients with an MI with obstructive CAD; several studies have shown that the mortality rate or re-infarction is not negligible following ACS with unobstructed CAD (21,23–27). A recent systematic review of patients presenting with suspected MI and unobstructed coronary arteries by Pasupathy et al. showed an overall all-cause mortality of 4.7% at 12 months.(28) Several recent studies have shown that additional imaging like cardiac magnetic resonance (CMR) may be particularly useful in determining the diagnosis. Accurate diagnosis helps to tailor medical treatment, for example the

diagnosis of a non-ischemic underlying etiology may obviate the need for anti-platelet and anti-atherosclerotic therapies.

Three possible etiologies explain the clinical presentation in up to 95% of cases of acute chest pain, elevated troponin and unobstructed coronary arteries (29–38)-MINOCA. These include: i) acute myocarditis, ii) acute MI and iii) cardiomyopathy, in particular Tako-Tsubo cardiomyopathy (TCM). All of these conditions can be easily diagnosed with an appropriately tailored CMR study.

CMR diagnostic accuracy is based on the use of a number of different sequences, which includes - long- and short-axis cine, and T2-weighted and late gadolinium enhancement (LGE) imaging repeated in the same slice positions as the cine imaging. These 3 sequences assess the presence of regional wall motion abnormalities and ventricular volumes calculation, presence and extent of myocardial oedema/inflammation and myocardial scar/fibrosis, respectively.

First-pass perfusion and T1 and T2 mapping sequences can be added depending on the clinical question or the research interest. This will result in a total scan duration time of ~45min. (39)

All of the 3 acute pathologies (myocarditis, MI or TCM) cause myocardial injury leading to edema. Edema in CMR corresponds to an increase in the T2 relaxation time which can be delineated with T2 weighted imaging. (40) There are various sequences available for delineation of myocardial edema. T2-weighted short-tau inversion recovery (T2-STIR) is the most commonly used sequence to image edema in clinical practice. However, T2-STIR image quality is easily degraded with respiratory motion or tachyarrhythmia, which are both common in patients with ACS and unobstructed coronaries. Newer sequences such as ACUT2E (cardiac unified T2 edema) and T2 mapping are less prone to such artefacts. However, a recent study by McAlindon et al. demonstrated that the different methods for detecting and quantifying myocardial edema are not interchangeable, and that T2 mapping was the most reproducible method, albeit this sequence comparison was done just in the context of STEMI (41).

Three CMR sequences have diagnostic role in patients suspected with myocarditis: 1) LGE sequences for detection of myocardial necrosis and/or fibrosis 2) T2-weighted images for assessment of myocardial edema 3) T1-weighted sequences before and after contrast injection for detection of myocardial hyperemia. Myocardial infarction can be diagnosed on CMR by identifying a subendocardial or transmural LGE pattern (42) whereas TCM can be diagnosed by the characteristic mid-apical myocardial edema with corresponding regional wall motion abnormalities and apical ballooning, but with no or only subtle LGE.

Although a number of retrospective and prospective clinical studies have reported the diagnostic role of CMR in this patient cohort, the diagnostic pick-up rate is variable. This could be attributed to the time delay between CMR imaging from the acute presentation, as well as the CMR sequences and imaging protocol used.

1.2.2.1 Role of CMR in Diagnosis - Acute Myocarditis

Several studies have shown that the commonest underlying etiology of patients presenting with suspected ACS and unobstructed coronary arteries is myocarditis. The prevalence of myocarditis is variable and ranges from 15 to 75% (29–38). This large variation is probably due to the CMR imaging sequences being used and the timing of the scan from the acute presentation. The use of T2-weighted images for assessment of myocardial edema/inflammation and imaging patients early from the onset of symptoms increases the diagnostic pick-up rate given that some abnormalities as myocardial edema/inflammation may be reversible and resolve with time. Use of T2-weighted images for assessment of myocardial edema and scanning the patients within 2 weeks from the onset of symptom increases the diagnostic pick up rate.(43)

The non-invasive imaging diagnosis of myocarditis and myocardial inflammation always represented a diagnostic challenge because diagnosis is based on indirect signs like myocardial swelling, wall motion abnormality and pericardial effusion, particularly with echocardiography.(44) Endomyocardial biopsy (EMB) still

represents the gold standard for the diagnosis of myocarditis. Recently, several studies have validated CMR against EMB, (31,45,46) suggesting that CMR can have a promising role in the diagnostic pathway of these patients. (47–52)

EMB is an invasive procedure and not widely available and has several limitations including low sensitivity and specificity due to sampling errors. This has fostered the increasing interest on the role of CMR in these patients. A recent Expert Position Statement of the European Society of Cardiology (ESC) confirms the important diagnostic role of CMR in patients with suspected myocarditis. (53) Whilst CMR cannot replace EMB, there is agreement that it can be offered in clinically stable patients prior to EMB. CMR guided EMB, ie obtaining the biopsy specimen from the LGE scar, can improve the diagnostic rate of the disease, as demonstrated by Mahrholdt et al. (54)

Recently, a consensus paper has defined the recommendations on the use of CMR in myocarditis (55) which led the establishment of the “Lake Louise criteria” diagnostic criteria. In particular, the CMR findings are consistent with the diagnosis of myocarditis if 2 of 3 sequences demonstrating myocardial edema, hyperemia and fibrosis are positive.

Novel parametric mapping techniques like, native T1 mapping, extracellular volumes of distribution (ECV) and T2 mapping, currently mainly used for research, have recently shown promising results in the diagnostic assessment of myocarditis. (56) Recent studies by Ferreira and Piechnik et al. (57,58) demonstrated that native T1 mapping has a superior diagnostic role compared to conventional T2-weighted imaging, and an equivalent performance to LGE. Native T1 mapping can also display the typical non-ischemic patterns in acute myocarditis, without the need for gadolinium contrast agents (59). Radunski et al. recently demonstrated the utility of ECV quantification, as a measure of interstitial fibrosis in both acute and subacute, severe myocarditis (60). They compared the diagnostic performance of T2, T1, and ECV as novel quantitative tissue markers compared to the Lake Louise criteria. ECV quantification together with LGE imaging significantly improved the diagnostic accuracy of CMR compared with the Lake Louise criteria. (60)

1.2.2.2 Role of CMR in Diagnosis -Embololic MI/ MI with Spontaneous Recanalisation

Acute MI with unobstructed coronary artery is a common clinical situation and is the second most common etiology in this cohort of patients (5-29%) (29–38). Several different patho-physiological mechanisms have been proposed to explain this phenomenon e.g. rupture or erosion of a vulnerable plaque (causing transitory occlusion that resolves spontaneously, without leaving any residual visible intracoronary lesion), and distal vessels or small-caliber side branches disease. Other mechanisms including distal embolisation, coronary vasospasm, inflammation or coronary dissections are rarely associated. Myocardial infarction can be diagnosed on CMR by identifying either a subendocardial or transmural LGE pattern in a typical coronary artery territory.(42) CMR can provide information on whether the myocardial infarction is acute/sub-acute or chronic. Acute ischaemic myocardial injury leads to myocardial edema, which can be delineated with T2 weighted imaging. Establishing the diagnosis in the presence of MI with unobstructed coronary arteries is very important, particularly so that appropriate management can be tailored. This can represent a plaque event or an extra-coronary embolic event. Review of coronary angiogram and coronary plaques, and excluding other sources of emboli (for example: exclude a patent foramen ovale as a potential contributor to a paradoxical embolic MI) often follows this diagnosis by CMR.

Patients with acute MI need long-term clinical follow-up and secondary atherosclerotic prevention treatment. In addition, CMR can provide further valuable prognostic information in this setting, including myocardial wall motion, global function, perfusion and viability.

1.2.2.3 Role of CMR in Diagnosis - Cardiomyopathy

Cardiomyopathy is the third common cause of suspected ACS with unobstructed coronary arteries. According to literature TCM is the most frequent and occurs in 10-15% of this patients group (29–35,38). Occasionally, dilated cardiomyopathy or

hypertrophic cardiomyopathy may also present with chest pain with unobstructed coronaries.

TCM or stress cardiomyopathy is a subtype of MI with unobstructed coronary artery, and defined by the characteristic wall motion abnormality that is, by definition, reversible and transient. The condition usually has a favorable prognosis compared to the other conditions. It is often, but not always, provoked by an emotional stress or respiratory distress. Several mechanisms have been hypothesized for TCM, including plaque disruption, multivessel spasm, baroreflex abnormalities, and catecholamine toxicity. It remains unclear whether TCM occurs due to one or multiple mechanisms in individual patients.

TCM is characterized by mid-cavity to apical regional wall motion abnormalities (“apical ballooning”) with sparing of the left ventricular basal segments. This can be identified by LV angiogram, as well as transthoracic echocardiography. The added diagnostic value of CMR is in its 1) high spatial resolution, 3D image acquisition, and 2) non-invasive myocardial tissue characterisation. The former results in a clear detection of cardiac chambers and endocardial contours, whilst the latter allows the detection of myocardial edema (markedly present in TCM) and myocardial scarring (usually absent in TCM). (61) Typically, T2-weighted sequences are used to image myocardial edema and it commonly identifies the presence of circumferential and transmural myocardial edema of the apical to mid-cavity myocardium matching with the regional wall motion abnormalities. (62) Since myocardial edema is a transient phenomenon, it is advisable that CMR imaging is carried out within the first few weeks from the acute presentation. Myocardial edema resolves in 2-3 months without any myocardial scarring and with complete functional recovery. (62) A few studies have shown the presence of subtle late gadolinium enhancement in TCM (63), but experimental data shows that delayed washout of gadolinium may be caused by increased interstitial water content such that associated with transient myocardial edema. (64) The subtle changes are called myocardial edema-related LGE and they do not represent myocardial necrosis. The distribution of myocardial edema

matching the wall motion abnormalities with no or subtle LGE helps in distinguishing TCM from myocardial infarction and myocarditis.

1.2.2.4 Risk stratification with CMR in ACS with unobstructed coronaries

ACS with unobstructed coronary arteries is a common clinical entity encountered in day-to-day clinical practice. The mean age of presentation is usually lower than ACS with obstructed coronaries, (65). Except for cigarette smoking, (66) the common risk factors for CAD such as hypertension, diabetes mellitus and hyperlipidemia are less present than in the obstructed coronary artery group. (67) ACS with unobstructed coronaries poses a clinical dilemma, as the underlying diagnosis is variable and often unclear. Accurate diagnosis is not only important for initiation of appropriate treatment, but may also have long-term implications for the patient. Contrary to popular belief, the 1-year mortality in the overall group was shown to be non-negligible in a recent systematic review.(28) Diagnosis is crucial as a completely normal CMR scan is associated with a good prognosis as demonstrated by the study by Chopard et al (34). CMR and its unique non-invasive myocardial tissue characterization do not just have a diagnostic role but it has a potential role in risk stratification.

1.2.2.5 Risk stratification in Myocarditis

Clinical presentation of myocarditis can be varied ranging from benign disease with preserved cardiac function to more aggressive form associated with severe LV/RV dysfunction (like giant cell myocarditis). Recent literature on myocarditis delineates its possible malignant side. Myocarditis was the third leading cause of sudden death after hypertrophic cardiomyopathy and congenital/atherosclerotic coronary artery disease, as demonstrated in a clinical case series of sudden deaths in young competitive athletes. (68) Myocarditis is responsible for 5% to 20% of sudden deaths as demonstrated in the autopsy studies of young adults. (69) It may also resolve spontaneously without specific treatment in patients presenting with mild symptoms

and minimal ventricular dysfunction.(53) In up to 30% of cases, biopsy-proven myocarditis can progress to DCM and is associated with a poor prognosis.(53) CMR with its superior tissue characterization property can delineate the severity of myocarditis, thereby guiding in the management and in risk stratification. A recent study by Grun et al has shown the presence of LGE is the best independent predictor of all-cause mortality and of cardiac mortality in 222 consecutive patients with biopsy proven viral myocarditis. (70) LGE performed better than the traditional markers like LV ejection fraction, LV end diastolic volume and NYHA symptom class. Moreover, normal CMR in patients with clinically suspected myocarditis, is associated with a good prognosis independent of their clinical symptoms and other findings. (71) Thus CMR may help to distinguish a benign from malignant form of myocarditis. Prompt CMR diagnosis of an aggressive myocarditis may led to in initiation of appropriate therapy like immunosuppressants, early referral for myocardial biopsy or help in MR guided biopsy. Response to immunosuppressive therapy has been reported mainly in chronic virus-negative forms, in giant cell myocarditis, and in active myocarditis defined as autoimmune (e.g. virus-negative and autoantibody positive).(53)

1.2.2.6 Risk stratification in MI

CMR can also help in risk stratification in MI. In addition to help achieving the diagnosis, the better tissue characterization properties allow accurate assessment of infarct size (LGE) and myocardial salvage. The area of myocardial edema delineated by T2-weighted CMR corresponds to the myocardial area at risk (AAR). The presence and extent of myocardial salvage can also be derived with CMR by subtracting the infarcted area from the AAR.(72) There is increasing data on the prognostic value of CMR derived infarct size and myocardial salvage. (73,74) Microvascular obstruction (MVO), characterized by hypoenhanced core within myocardial infarction scar (hyperenhancement) on rest first-pass perfusion or LGE imaging, can occasionally be demonstrated. The presence and extent of MVO after AMI is associated with adverse LV remodeling and poor clinical outcome (75–77), and myocardial segments with MVO at presentation are more likely to develop wall thinning and fail to demonstrate functional recovery. (78) Nijveldt et al confirmed that MVO in LGE

proved a more powerful predictor of global and regional functional recovery than the transmural extent of infarction.

CMR can potentially diagnose the complications of MI. CMR is superior to echocardiography for the identification of ventricular thrombi, particularly when they are small and apical. They are easily identifiable early after contrast administration when both the cavity and the myocardium still appear bright, whilst the thrombus appears hypointense (lack of contrast uptake given that it is avascular).(79,80) CMR is also able to detect other complications of MI including ventricular aneurysm, pseudoaneurysm, papillary muscle infarction with subsequent mitral regurgitation etc.

1.2.2.7 Risk stratification in TCM

Although TCM is usually considered to be a benign reversible condition, its arrhythmic risk is increasingly recognized. There are promising new CMR analyses which may help to risk stratify the patients with potential higher arrhythmic risk. (81)

Deep T-wave inversion and QTc interval prolongation on ECG may be observed in TCM.(82,83) Malignant arrhythmias include torsades de pointes (TdP) caused by repolarization abnormalities and QTc prolongation, can be seen in up to 8% of cases. (84) In one meta-analysis, sudden cardiac death (SCD) after TCM has been reported in 1.1% during the index episode, with a further 0.5% of patients suffering a SCD weeks to months later. (85) The study primarily looked at the relationship between TCM and ventricular arrhythmias, reviewing a total 816 published cases. VF was reported in 15 cases (prevalence of 1.8%) and VT was reported in 18 (2.2%). (85) The T-wave inversion and QT interval prolongation in typical TCM is thought to be caused by an intra-cardiac gradient (apico-basal) of myocardial edema which, in turn, gives rise to regional dispersion of action potential durations (86). A study by Perazzolo Marra et al. looked at the ECG and CMR findings in 20 consecutive TCM patients. A linear correlation of the apical-basal ratio of T2-weighted signal intensity with ECG repolarization indices such as negative T-wave magnitude, sum of the amplitudes of negative T-waves, and maximum corrected QT interval has been shown.(62) Interestingly, the repolarization changes were unrelated to either late

gadolinium enhancement or quantitative cine parameters. Hence, the T2-weighted signal intensity gradient can be potentially used as a marker of malignant arrhythmia.

CMR can also provide additional information on the presence of LV apical thrombus, valvular abnormalities and LV outflow tract obstruction. Some of these findings are also directly linked to adverse prognosis.

1.2.3 ST-elevation myocardial infarction (STEMI)

The morbidity and mortality from STEMI varies based on patient- and treatment-factors. Infarct size is directly associated with mortality. Patients with an infarct >12% of the LV has 7% mortality at 2 years compared to 0% with an infarct <12%. (87) The amount of transmural scar can predict adverse LV remodeling, with significant additional predictive value over troponin.(88) LGE derived infarct size is a stronger predictor of all-cause mortality than LVEF and LV volumes in healed MI patients. (89) Transmurality is associated with worse outcome, and CMR derived acute infarct size is a stronger predictor of future events. (90) Several methods exist to quantify transmural, including semi-automated techniques (mainly used in research). (91) In reperfused STEMI patients time to reperfusion determines the extent of reversible and irreversible myocardial injury as assessed by CMR. Particularly, salvaged myocardium is markedly reduced when reperfusion occurs >90 min of coronary occlusion. (92)

Both CMR derived infarct size and myocardial salvage have prognostic importance (73,74). Myocardial oedema is maximal and constant over the first week post MI, thereby providing a window for the retrospective evaluation of AAR whereas LGE recedes over time with corresponding recovery of function, indicating that acutely detected LGE does not necessarily equate with irreversible injury and may severely underestimate salvaged myocardium. (93)

CMR is not routinely performed in all STEMI patients. However, it provides an opportunity to further understand the degree of LV dysfunction and underlying myocardial damage.

1.2.3.1 Microvascular obstruction

This is a hallmark of acute myocardial damage, encountered in up to 30% of patients with STEMI (94). The presence and extent of MVO after AMI is associated with adverse LV remodeling and poor clinical outcome (75–77), and myocardial segments exhibiting MVO are more likely to develop wall thinning and not regain function. (78) MVO is a powerful predictor of global and regional functional recovery than the transmural. (95) CMR derived infarct size and MVO provide independent and incremental prognostic information in addition to clinical risk scores and LV ejection fraction. (96) In another study MVO was an independent predictor of MACE and cardiac death, whereas infarct size was not. (97) de Waha et al showed that the ratio of MVO/infarct size is a more powerful predictor for long-term outcome than either parameter alone.(98)

1.2.3.2 Intramyocardial haemorrhage

Intramyocardial haemorrhage is another sequelae of microvascular damage, appearing as hypo-intense areas in the rest first-pass perfusion and LGE images, similarly to MVO. The distinctive aspect of IMH compared to MVO is the hypointense signal also in the T2-weighted images caused by the haemoglobin breakdown products, not observed in MVO. Therefore, T2-weighted images are essential for distinguishing IMH from MVO.

Infarct size, myocardial salvage, MVO and IMH measured by CMR are increasingly used as surrogate endpoints in clinical trials of acute myocardial infarction and reperfusion strategies.(99) For example, the EXPIRA trial showed that in STEMI, thrombectomy prevents thrombus embolization and improves microvascular

integrity by reducing the presence and extent of MVO and infarct size measured by CMR (100). Another study showed, IMH can predict MACE and adverse remodeling however the study failed to show an improvement of the predictive value of LGE-CMR by adding T2 imaging.(101)

Whether CMR is the best non-invasive imaging surrogate marker to assess improvement after treatment is debatable and further studies are needed to clarify this aspect.

1.2.3.3 STEMI with multivessel disease

It is estimated that 40-65% of the patients presenting with STEMI have MVD. (102,103) The current ESC guidelines on STEMI advise a stress imaging guided approach (including CMR) to guide complete revascularization in bystander disease detected at time of PPCI. Adenosine stress CMR performed 1-5 days post-PPCI has been shown to be safe and effective for detection of ischaemia in non-culprit coronary stenosis with excellent overall diagnostic accuracy. (104). Dastidar et al demonstrated that, less than 40% patients undergoing PPCI with moderate to severe MVD need further revascularization when a stress CMR gatekeeper approach was used. (105) The role of invasive and non-invasive imaging in this patient group is currently being investigated and debated.

1.2.3.4 Complications of ACS

CMR is superior to echocardiography for the identification of ventricular thrombi. They are easily identifiable early after contrast administration when both the cavity and the myocardium still appear bright, whilst the avascular thrombus does not take up contrast and appears hypointense.(79,80) CMR is also able to detect other complications of MI including ventricular aneurysm, pseudoaneurysm, papillary muscle infarction with subsequent mitral regurgitation and ventricular septal defects that could lead to cardiac rupture.(106) Figure 6

CMR can also detect RV involvement in acute MI (107). Early post-infarction RV ischaemic injury is common and is characterized by myocardial oedema, LGE, and functional abnormalities. RV injury is not limited to inferior infarcts but also common in anterior infarcts(108). RV infarction detected by CMR is a strong and independent predictor of clinical outcome after acute reperfused STEMI. (109)(110)

1.2.3.5 Myocardial viability

Numerous studies have demonstrated that LV dysfunction in patients with CAD may be reversible (myocardial stunning or hibernation). (111) Hibernating myocardium(viability) is in a down-regulated functional state as a consequence of chronic ischaemia, but maintains the possibility to regain function if coronary blood flow is restored. Stunning is dysfunction related to acute ischemia. Viability assessment may be useful in acute coronary syndrome for example in delayed presentation of STEMI or in bystander coronary artery disease.

LGE CMR allows the differentiation of viable from non-viable myocardium, predicting which dysfunctional myocardial segments could improve after successful revascularization. However, extensive LV remodeling (LV end-systolic volume >141ml) may limit functional improvement after revascularization, with negative long-term prognostic effects, despite the presence of viability.(112)

A meta-analysis demonstrated significant survival benefit of revascularizing patients with viable myocardium over medical management, with no significant difference between the treatments in non-viable myocardium(113), thereby establishing the importance of viability. Assessing myocardial viability to guide management in chronic ischaemic systolic LV dysfunction is recognized in the 2014 ESC/EACTS guidelines on myocardial revascularization(114).

The STICH trial recently questioned the role of viability, showing that in patients with CAD and LV dysfunction the assessment of myocardial viability did not identify patients with a differential survival benefit from CABG, as compared with medical therapy alone. (115) However, viability imaging was at the physician's discretion,

several modalities were used (but no CMR) and the definition of viability was questionable. Other studies are underway to clarify the role of viability in patients with LV dysfunction.

Multiple imaging modalities are available to assess viability, such as dobutamine stress echocardiography, SPECT and positron emission tomography (PET)(113). The ESC/EACTS guidelines on myocardial revascularization(114) recognize the high diagnostic accuracy of CMR for assessing the transmural extent of myocardial scar combined with its ability to assess contractile reserve. CMR has a high spatial resolution, enabling to detect up to 1g of infarcted myocardium (upto 10g with SPECT) (116). In addition, the reproducibility of CMR assessment of chronic infarct is excellent(117). However, the guidelines also concede that the overall differences in performance between modalities are small and that local experience and availability are likely major determinants (114).

Two CMR parameters mainly used to assess myocardial viability: infarct transmural extent with LGE, and contractile reserve with dobutamine CMR. In a study on patients with ischaemic LV dysfunction, the transmural extent of LGE predicted LV functional recovery after revascularization. (118) In particular, the absence of LGE corresponded to a 78% chance of recovery at 3 months compared to 10% with 51-75% transmural extent, falling to 2% with >75% transmural LGE. However, in 1-50% transmural extent, the chance of functional recovery was indeterminate and approximately 50%. Similar results were reproduced by other groups (119).

Low dose dobutamine CMR is superior to LGE-CMR as a predictor of segmental recovery particularly in segments with 26-75% LGE. (120)

End-diastolic wall thickness (EDWT)

Myocardial thinning often represents myocardial scarring from previous infarction (121) with EDWT <6mm carrying a low probability of post-revascularisation functional recovery (122) but thinned myocardium could also represent hibernating viable myocardium (123). Therefore, absolute EDWT (thinning) per se should not

represent a marker of viability. However a study by Baer et al demonstrated that the presence of significantly reduced LV end diastolic wall thickness reliably indicates irreversible myocardial damage.(124)

Regional wall motion abnormality (RWMA) / contractile reserve

Regional wall motion abnormalities is only present when the transmural infarct extension is >50% (125,126) and not in the presence of smaller infarctions. Thus, RWMA per se underestimates infarct size.

Stress CMR with dobutamine follows the same protocol used in echocardiography: the agent is administered at increasing doses until target heart rate is achieved (might require the administration of atropine). In the presence of a flow-limiting coronary stenosis, the myocardium will display new RWMA on cine images as a surrogate for ischaemia. Conversely, improvement of RWMA during low-dose dobutamine represents a marker of myocardial viability (127). The sensitivity and specificity of dobutamine CMR is superior to dobutamine stress echocardiography. (128) Quantifying RWMA by myocardial tagging (129)(130) or post-processing feature tracking software can increase diagnostic accuracy(131).

A meta-analysis highlighted the importance of integrating CMR parameters for viability assessment, (132) demonstrating that LGE provided the highest sensitivity (95%) and negative predictive value (90%), whereas low-dose dobutamine offered the best specificity (91%) and positive predictive value (93%). A combination of viability parameters (transmurality, contractile reserve, EDWT, unenhanced rim thickness and segmental wall thickening of the unenhanced rim) may be a better predictor of recovery. (133)

The work presented on this chapter has been published in the following 3 published papers. I was the first author in all those 3 papers with Dr Chiara Bucciarelli-Ducci as the senior author:

- **Dastidar AG, Rodrigues JCL, Baritussio A et al. MRI in the assessment of ischaemic heart disease. Heart 2016 Feb;102(3):239-52 (134)**
- **Dastidar AG, Rodrigues JCL, Ahmed N et al. The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. Curr Cardiovasc Imaging Rep. 2015;8(8):28 (135)**
- **Dastidar AG, Frontera A, Palazzuoli A, et al. TakoTsubo cardiomyopathy: unravelling the malignant consequences of a benign disease with cardiac magnetic resonance. Heart Fail Rev. 2015 Jul;20(4):415-421 (136)**

2 Study hypothesis and aims

2.1 CMR in Myocardial infarction with non-obstructed coronary artery

CMR is an established diagnostic imaging tool in the assessment of MINOCA. The following research questions are investigated

2.1.1 Optimum timing of CMR

The diagnostic utility of CMR in MINOCA has been demonstrated in various clinical studies. However, the importance of timing of CMR remains unknown. The study aimed at establishing the optimum timing of CMR.

2.1.2 Clinical impact of CMR in MINOCA

The clinical impact of CMR in MINOCA remains unknown. The study aimed at identifying the clinical impact of CMR i.e. change in the diagnosis and the change in treatment.

2.1.3 Prognostic role of CMR in MINOCA

There is paucity of data on the exact prognostic role of CMR in MINOCA. The study aimed at identifying the prognostic impact of CMR and conventional risk markers in MINOCA

2.2 New CMR techniques in ST segment elevation myocardial infarction

Multiparametric CMR including gadolinium enhancement in the setting of STEMI can provide invaluable information. However, the use of gadolinium is restricted in conditions like kidney impairment. Newer non-contrast native T1 and T2 mapping may obviate the need for gadolinium.

2.2.1 Widespread tissue injury in STEMI

Histological studies have shown that the tissue injury in STEMI is not restricted to the infarct artery related territory. (137) The study aimed at demonstrating in-vivo the presence of widespread myocardial changes including the remote myocardium in patients with AMI via advanced CMR myocardial tissue characterization (T1 and T2 mapping) without the need for gadolinium contrast. We also looked at the associates of high remote myocardium T1.

2.2.2 Non contrast assessment of viability via native T1-mapping

Viability assessment remains the keymost indication for CMR in management of IHD.

The most commonly used sequence for viability assessment in routine clinical practice is via LGE transmuralty.(118) The aim of the study was to compare the performance of non-contrast native segmental T1 mapping in quantifying the TEI/myocardial scarring with LGE in chronic as well as acute MI patients using a 1.5T CMR.

3 Methods

3.1 Study Population

There are 2 main cohort of patients included in this thesis – A) MINOCA group and B) the STEMI group.

3.1.1 MINOCA cohort:

In this longitudinal observational study, consecutive patients presenting with MINOCA(chest pain, elevated troponin and non-obstructed coronary arteries) as per the new ESC STEMI Guideline(8) and undergoing CMR were included and followed up prospectively.

Exclusion criteria were:

- general contraindications to MRI,
- patients admitted with suspected heart failure,
- renal impairment with eGFR <30,
- patients admitted with arrhythmic events at presentation.

The study was performed at a large cardiothoracic tertiary centre in the South-West of England; data were collected on consecutive patients scanned from September 2011 to December 2015. Patients were identified either presenting with STEMI or NSTEMI.

Non-obstructed coronaries were defined as:

- TIMI III flow;
- <50% stenosis in any coronary artery.(8)

Troponin T level <14ng/L was considered normal. 'False positive' troponin possibilities: a single troponin elevation (<5x upper limit of normal), which was not repeated during the admission or if a single elevated troponin was followed by a second normal troponin level within 24 h were excluded from study. (5) The study was reviewed and approved by the local Institutional Review Board.

3.1.2 STEMI Cohort

Thirty successfully reperfused STEMI patients (mean age 61±10years and 80% males) and 20 healthy volunteers were recruited. All patients were diagnosed with STEMI according to guidelines. (6,138)

Exclusion criteria were:

- general contraindications to MRI,
- chronic atrial fibrillation,
- renal impairment with eGFR <30,
- cardiogenic shock.

This study was approved by the local ethics committee. All patients gave informed written consent. The acute STEMI patients were recruited to the Myocardial Oedema in ST Segment Elevation Myocardial Infarction study NCT 01897350 (www.clinicaltrials.gov). For comparison with acute revascularised STEMI 20 healthy volunteers and 30 patients with previous myocardial infarction were included.

3.2 Funding

This project was supported by a University Hospitals Bristol NHS Foundation Trust PhD Clinical Research Fellowship and David Telling Charitable Trust Grant.

3.3 General CMR physics and methodology

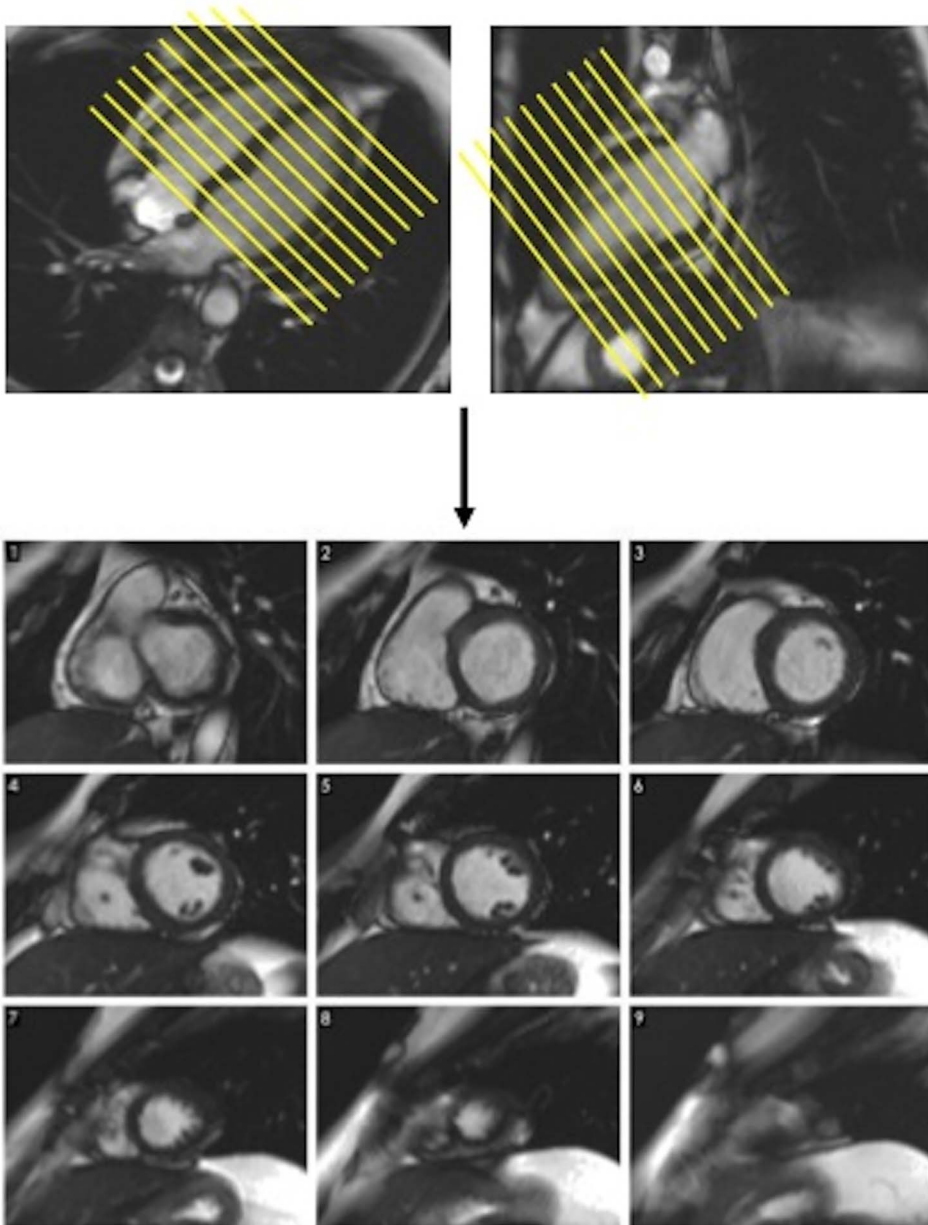
3.3.1 CMR imaging techniques

The cornerstone of CMR is its multi-parametric nature, i.e. its ability to assess multiple aspects of myocardial structure and function in a single examination with the aid of various imaging techniques. The combination of techniques used is tailored to the clinical question. Individual study protocols are described in details in the methods section of the following chapters. In the following section there is an overview of the commonly used CMR sequences.

3.3.1.1 Cine imaging

CMR is the current non-invasive gold standard method to measure left and right ventricular (LV and RV) volumes and ejection fraction (139,140). For CMR volumetric assessment, the ventricles are sliced from base to apex and the endo- and epicardium subsequently contoured. (**Figure 3-1**) Therefore it is truly 3 dimensional without relying on geometrical assumptions, unlike 2D echocardiography. However the 3rd axis information is limited compared to 3D echocardiography or 3D Multi Slice CT. Both the CMR long- and short-axis views are similar to echocardiography, as well as the myocardial segmental nomenclature (except the 17th segment apical cap, usually omitted in echocardiography). (141)

Figure 3-1 Top panel shows the four-chamber and two-chamber cines. Lower panel (1–9) short-axis cine dataset covering the heart, obtained by cutting the heart from base to apex.



Steady State Free Precession (SSFP) is the sequence of choice for cine imaging due its clear definition of endocardial and epicardial borders. Regional LV/RV function can be analysed visually by documenting the presence and extent of segmental wall motion abnormality (hypokinesia/akinesia/dyskinesia) as in echocardiography (142), or quantitatively by measuring wall thickening, and myocardial strain. (143) Cine CMR can also be used during low- and high-dose dobutamine to assess myocardial viability and inducible ischaemia, respectively. (144) (145,146)

3.3.1.2 T2-Weighted Imaging

CMR can detect myocardial oedema, a hallmark of acute inflammation using T2-weighted imaging. Myocardial oedema is a reversible phenomenon, progressively reabsorbed over time (<3 months).

In the setting of ACS, myocardial oedema by CMR has been validated as the myocardial area at risk (AAR) vs the gold-standard fluorescent microspheres. (147)

The presence and extent of myocardial salvage can be derived with CMR by subtracting the infarcted area measured by late gadolinium enhancement (LGE) from the AAR. Both AAR and myocardial salvage can be assessed retrospectively shortly after the acute event. (72)

T2-weighted short-tau inversion recovery (T2-STIR) is the most commonly used oedema imaging sequence. The different myocardial oedema sequences available are not interchangeable, and T2 mapping being most reproducible (41).

The assessment of the oedema images is usually done visually, but semi-automated image signal intensity methods are available (useful as surrogate end-points for clinical trials). (148)

3.3.1.3 Early and Late Gadolinium Enhancement (LGE) Imaging

This T1-weighted technique is the cornerstone of myocardial tissue characterization. Early gadolinium enhancement can demonstrate oedema and late gadolinium enhancement can demonstrate the presence and extent of myocardial scarring.

In brief, the gadolinium-chelate contrast agent administered intravenously promptly diffuses into the extracellular myocardial compartment. In normal myocardium, the contrast quickly washes in and out of the myocardium. The presence of myocardial scarring results in increased extracellular space, where the contrast accumulates with longer washout time relative to normal myocardium **Figure 3-2**. The accumulation and distribution of the contrast agent in the diseased myocardium follows the pathophysiological process of the underlying condition. In IHD, the myocardial ischaemic-necrotic wave-front phenomenon starts in the

subendocardium becoming progressively more transmural with the ischemic time. Therefore, in IHD the LGE pattern can be either subendocardial or transmural, with the infarcted myocardium appearing as a hyper-intense (bright) area (accumulation of contrast) and the normal myocardium as a hypo-intense (no accumulation of contrast).

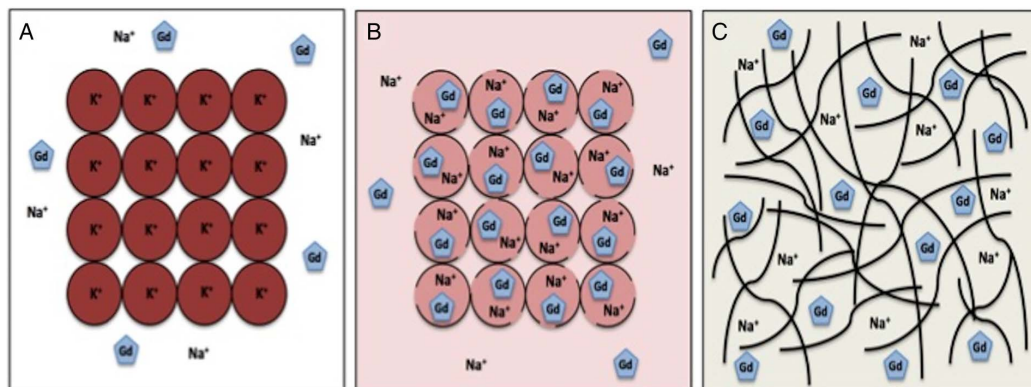


Figure 3-2 Gadolinium kinetics in normal myocardium and acute and chronic myocardial infarction. (A) Normal myocardium with an intact cell membrane. Gadolinium washes in and then promptly washes out of normal myocardium. (B) Acute myocardial infarction with ruptured cell membrane. Gadolinium washes out of acutely infarcted myocardium less quickly than normal due to an expanded volume of distribution as a result of disruption to the cell membrane. (C) Chronic myocardial infarction with collagen matrix scar formation. Gadolinium washes out of chronic myocardial infarction less quickly than normal due to increased interstitial space within the collagen matrix scar. K+=potassium ion; Na+=sodium ion; Gd, gadolinium. Adapted from Kim et al (149)

Contrast-enhanced fast spin echo T1-weighted MR during first few minutes after injection can be used to assess experimentally induced myocardial hyperemia and to detect muscular inflammation. Accordingly, the purpose of myocardial early gadolinium enhancement ratio (EGEr) is to detect an overall increased volume of gadolinium distribution into the intravascular and interstitial space during the early washout period.

LGE volume changes, in the minutes following contrast administration in acute but not in chronic MI. In acute infarct transmuralty 25 minutes post-contrast injection better predict infarct size and functional recovery. (150)

In the setting of acute MI, LGE imaging can also detect areas of hypo-intensity within the bright infarcted area, representing areas of microvascular obstruction (MVO), precluding entry of gadolinium into these areas.

3.3.1.4 Native T1 and extracellular volume fraction quantification (ECV)

Both native T1 and ECV are new technical developments offering an unprecedented opportunity to quantify changes in myocardial intracellular and extracellular compartments in a non-invasive manner, bringing a new dimension to myocardial tissue characterization beyond conventional LGE imaging.

Whilst alteration in native T1 may result from processes affecting the intracellular and/or extracellular compartments of the myocardium, ECV specifically quantifies expansion of the interstitial space as well as the vascular compartment. Currently, these sequences are mainly used for research but their use for improved diagnosis and prognostication is promising (151).

3.4 CMR methodology

In patients with IHD, a standard CMR imaging protocol includes both cine and LGE imaging; myocardial edema sequence is added to confirm the presence/absence of myocardial oedema. In addition, stress/rest first-pass perfusion can help to delineate the presence of inducible myocardial ischemia (**Table 3-1**). A typical CMR scan duration is ~45min (Figure 3).

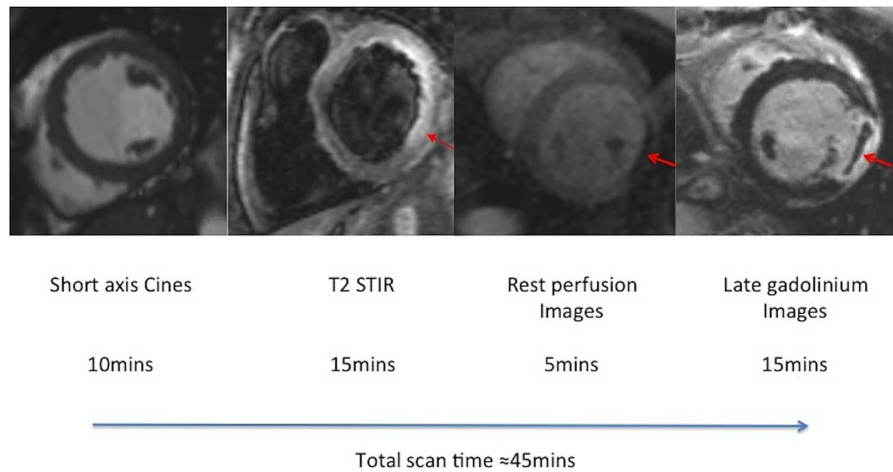


Figure 3-3 A case of acute STEMI with culprit diagonal coronary artery. The short axis cines showing the wall motion abnormality, T2 short- τ inversion recovery (STIR) imaging showing myocardial oedema or area at risk (arrow), rest perfusion showing early microvascular obstruction (arrow) and late gadolinium imaging showing lateral wall transmural enhancement with microvascular obstruction (arrow).

Table 3-1 CMR protocol for Acute Coronary Syndrome (39)

	Clinical application
<i>(A) Acute MI or acute coronary syndromes</i>	
1. Cines (short and long axis)	LV function Ischaemia/viability (during dobutamine)
2. Advanced tissue characterisation sequences (eg, T2 weighted imaging, T1 mapping)	Myocardial oedema
3. Optional—first pass perfusion at rest Consider stress in bystander disease assessment	MVO Ischaemia
4. Early gadolinium enhancement	MVO Thrombus
5. Late gadolinium enhancement	Viability Infarct size

3.4.1 Comparison with other imaging modalities

Table 3-2 summarises the relative merits and demerits of the different functional imaging modalities available, highlighting the superiority of CMR.

Table 3-2 Comparison of different functional imaging modalities in the assessment of IHD (CMR vs Echo vs SPECT)

	CMR	Echo	SPECT
Ejection fraction	+++	++	+
RWMA	+++	++	—
Wall thinning	++	+	—
Myocardial oedema	++	—	—
Viability	+++	++	+++
MVO	+++	—	—
Thrombus	++	+	—
Valve assessment	+	+++	—
RV	+++	++	+
Ischaemia assessment			
Increased BMI	++	+	++
Female	++	++	+
Adenosine	++	+	++
Dobutamine	++	++	++
Exercise	(+)	+++	++

BMI, body mass index; CMR, cardiac MRI; IHD, ischaemic heart disease; MVO, microvascular obstruction; RV, right ventricle; RWMA, regional wall motion abnormality; SPECT, single-photon emission computed tomography.

3.4.2 Limitations of CMR

CMR is a routinely used cardiac non invasive imaging modality. However, there are few contra-indications of CMR. Table 3-3 highlights the common contraindications of CMR.

Table 3-3 Contraindications of CMR

	Absolute contraindication	Relative contraindication
MRI	<ul style="list-style-type: none"> ▶ Intracranial aneurysm clips ▶ Automated implantable cardiac defibrillator (ICD) ▶ Non-MR conditional pacemaker ▶ Pacing dependent patient ▶ Cochlear, otological or ear implant ▶ Metallic intraocular foreign body ▶ Neurostimulator ▶ Non-MR conditional monitoring devices ▶ Non-MR conditional support devices 	<ul style="list-style-type: none"> ▶ Clinically unstable patients ▶ Long-stem joint prosthesis (at 3 T only) ▶ Severe claustrophobia
Gadolinium-chelate contrast agent	<ul style="list-style-type: none"> ▶ Previous anaphylactic reaction to gadolinium contrast ▶ Known nephrogenic systemic fibrosis (NSF) 	<ul style="list-style-type: none"> ▶ Renal impairment (eGFR <30 mL/min/1.73 m²) ▶ Hepatorenal syndrome ▶ Pregnancy

The work presented in this chapter has been published in the following review article.
I was the first author in the paper with Dr Chiara Bucciarelli-Ducci as the senior author:

- **Dastidar AG, Rodrigues JCL, Baritussio A et al. MRI in the assessment of ischaemic heart disease. Heart 2016 Feb;102(3):239-52 (134)**

4 CMR in Myocardial infarction with non obstructed coronary arteries

4.1 *Time to CMR in MINOCA*

4.1.1 Introduction

Acute coronary syndrome (ACS) is one of the leading causes of mortality and morbidity, worldwide.(152) Definite diagnosis of ACS is crucial for ensuring appropriate patient management. As per the international guidelines, patients presenting with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) proceed to immediate or inpatient coronary angiography, respectively, with the aim to identify and treat a culprit coronary artery occlusion or stenosis. However, in 7-15% of these patients no significant coronary obstruction is identified, representing a diagnostic dilemma, resulting in uncertainty regarding future management.(21)(15)

The underlying patho-physiological mechanisms occurring in patients presenting with chest pain, elevated troponin and unobstructed coronaries are complex and multifactorial. In the European Society of Cardiology (ESC) guidelines on the management of troponin positive ACS with unobstructed coronaries there is no definite recommendation.(4) A recent review article by Niccoli et al described the potential mechanisms and proposed a management algorithm for this cohort.(153) Patients with unobstructed coronaries are thought to have a better prognosis, therefore they do not always receive appropriate secondary prevention medications.(22) However, recent studies suggest that all-cause mortality may be as

high as 4.7% at 12 months.(21,23,28,154) Confirmation or exclusion of myocardial infarction by Cardiac magnetic resonance (CMR) facilitates tailoring of medical therapy, ensuring appropriate long-term modification of risk for those with evidence of infarction and minimising exposure to anti-platelet therapy and the associated bleeding risks for those with a non-coronary aetiology to their presentation. Few previous studies have shown that CMR can identify the underlying diagnosis, most commonly: acute/chronic myocarditis, acute MI with spontaneous recanalization/embolus, stress cardiomyopathy (Tako-Tsubo) or other cardiomyopathies.(29,30,32–34,36,37) Only in a small proportion of cases, CMR is unable to identify any abnormalities, but they have a good prognosis.(34) All of these studies have a common limitation of a relatively small sample size.(37) Also, importantly, CMR was performed in a highly variable time frame from the patients' acute presentation.

The present study aimed at identifying the difference in “early” CMR (performed ≤ 2 weeks from presentation) vs “late” CMR (performed >2 weeks from presentation) in establishing a final diagnosis

4.1.2 Methods

4.1.2.1 Study population

Consecutive patients with new-onset chest pain, elevated troponin levels and unobstructed coronaries, demonstrated by invasive coronary angiography or multi-slice coronary computed tomography, referred for a CMR were included in the study. The study, was performed at a large cardiothoracic tertiary centre in the South-West of England, data was collected on consecutive patients scanned from September

2011 to July 2014. A total of 204 patients were identified. Unobstructed coronaries were defined as: TIMI III flow; <50% stenosis in any of the coronary artery.(155) Troponin T level <14ng/L was considered normal. The study was reviewed and approved by the local Institutional review Board.

4.1.2.2 CMR protocol

CMR was performed on 1.5T, Magnetom Avanto (Siemens Medical Solutions, Erlangen, Germany). A comprehensive CMR protocol was adopted which included cine, myocardial oedema and myocardial scarring imaging. In particular, cine images were performed using a steady-state free-precession sequence acquired in three long axis planes and a stack of short axis images covering the left ventricle (LV). T2 weighted (T2 STIR) sequence was used for the oedema images and was acquired in the same planes as the cine images. Intravenous gadolinium-chelate contrast agent (gadobutrol) was administered at a dose of 0.1 mmol kg^{-1} of body weight. Images were acquired 2-3 min after contrast injection (early gadolinium). Late gadolinium enhancement (LGE) images were acquired 15min after contrast injection using an inversion recovery segmented gradient echo sequence. (39,148)

4.1.2.3 CMR analysis

Each CMR scan was analysed and reported by a consultant with >10 years of CMR experience and certified CMR level 3 by the ESC. Myocarditis was diagnosed based on fulfilling two out of three Lake Louise Criteria (55): STIR T2-weighted sequences detecting myocardial oedema; early gadolinium sequences detecting hyperaemia; epicardial or mid-myocardial LGE (55). MI was diagnosed based on territorial

subendocardial and/or transmural LGE. Tako-tsubo cardiomyopathy was diagnosed based on the STIR T2-weighted images detecting myocardial oedema and regional wall motion abnormality in the mid-cavity or apical distribution with minimal or no LGE; all in accordance with the modified Mayo Clinic criteria.(156) Dilated cardiomyopathy, hypertrophic cardiomyopathy and cardiac amyloidosis were detected based on specific tissue characteristics previously described.(157–159) The diagnostic rate of CMR performed within 7days of presentation was also analysed.

4.1.2.4 Statistical analysis

Data are presented as percentages and mean±standard deviation as appropriate.

Differences in proportions are tested with a χ^2 test or Fisher's exact test, and differences in normally distributed continuous variables with a Student's t test.

Propensity matching was performed to minimise any selection bias due to the differences in clinical characteristics between early and late CMR groups. For each patient in the cohort, a propensity score indicating the likelihood of an early CMR was calculated by the use of a non-parsimonious multivariable logistic regression model. Covariates included in the logistic regression model to calculate the propensity score were age, gender, family history of ischaemic heart disease (IHD), diabetes mellitus, smoking status, hypertension, presentation (NSTEMI or STEMI), troponin T level and LV systolic function. To identify matched pairs of patients undergoing early or late CMR, a 1:1 optimal match with a ± 0.26 caliper and no replacement was used.

SPSS Version 23 (IBM Corp, Armonk, NY) was used for statistical analysis. Probability values were two-sided, and values of $p < 0.05$ were considered significant.

4.1.3 Results

Clinical characteristics of the overall population ($n=204$) and patient groups are summarized in Table 1. The mean age of the cohort was 55 ± 17 years (51% male). Generally, there was a low prevalence of cardiovascular risk factors (Table 1). The mean time delay between acute presentation and CMR was 32 days (range 1-150 days).

Table 4-1 Baseline study population, early vs late CMR population characteristics.

	Total	Entire cohort			Propensity matched		
Characteristics	population (n=204)	Early CMR (n=98)	Late CMR (n=106)	P-value	Early CMR (n=58)	Late CMR (n=58)	P-value
Mean age (SD)	56 (17)	56(18)	57(17)	0.71	56(17)	53(17)	0.43
Male sex %	51	54	48	0.4	53	50	0.85
Family history of IHD %	3	3	4	1	5	5	1
Diabetes %	6	4	9	0.25	5	9	0.72
Hypertension %	17	12	22	0.09	14	17	0.8
History of smoking %	7	6	8	0.78	7	7	1
LV function Echo %							
Normal	62	53	71	0.009	60	73	0.23
Mild	20	20	19	0.86	15	15	1
Moderate	12	17	7	0.05	15	7	0.23
Severe	6	9	4	0.15	10	5	0.49
Mean troponin T ng/L	640	762	477	0.003	708	506	0.13
Presentation as STEMI %	19	23	15	0.15	22	16	0.48
Mean interval in days (presentation and CMR)	32	5	56	<0.0001	5	55	<0.0001
Diagnosis %	70	84	57	<0.0001	88	50	<0.001
Clinical Impact %	66	73	59	0.04	76	51	0.01

4.1.3.1 Overall cohort

Overall, CMR provided a diagnosis in 143/204 (70%) patients, whilst in the remaining 30% of patients CMR was normal (no abnormalities detected). Myocarditis was the most common diagnosis, comprising 54 (26.5%) patients of the whole patient cohort, closely followed by MI (n=53, 26%). Among the cardiomyopathies excluding myocarditis (16.5% of patients) Tako-Tsubo was the pathology most commonly identified (9% of patients). One patient was identified as having severe valvular dysfunction and was classified as 'other' diagnosis.

An "early" CMR was performed in 98 patients (48%) and a "late" CMR in 106 patients (52%). The diagnostic yield was significantly higher for the "early" vs "late" CMR (84% vs 57% $p<0.0001$). Myocarditis (33%) was the most common diagnosis in the "early" group, whereas MI (26%) was the most prevalent in the "late" group. The pick-up rate of myocarditis and cardiomyopathy were significantly higher in patients undergoing "early" CMR compared with "late" CMR (33% vs 21%, $p=0.04$), whereas there were no differences in the prevalence of MI (26% both groups, $p=1.0$). The prevalence of a normal scan was significantly higher in the "late" CMR group (43% vs 16% $p<0.0001$).

Further subgroup analysis revealed a diagnostic rate of 87% when the CMR scan was performed ≤ 1 week (n=78) from admission (vs 84% when done ≤ 2 weeks, $p=0.40$).

4.1.3.2 Propensity score matched cohort

Propensity score matching identified 58 pairs of early and late subjects. Baseline characteristics are summarized in Table 1. The results confirmed the significantly higher diagnostic yield in the “early” vs “late” CMR propensity matched group (88% vs 50% $p<0.0001$). Myocarditis (33%) was the most common diagnosis in the “early” group, whereas MI (22%) was most prevalent in the matched “late” group. The prevalence of MI was not different in the “early” and “late group (22% vs 26% respectively, $p=0.83$).

4.1.4 Discussion

Early invasive management of troponin positive ACS has revealed a significant cohort of patients (7-15%) with unobstructed coronaries on angiography.(21)(15) This creates a diagnostic dilemma, hindering decisions on medical management. It is important to identify a cause for the acute presentation in order to adopt appropriate management. CMR is a non-invasive imaging technique that is able to identify a diagnosis in these patients in up to 70% of cases. Our study has demonstrated, in a large cohort of patients, that CMR performed early (≤ 2 weeks from acute presentation), improves the diagnostic rate, with a consequent impact on treatment.

The diagnostic role of CMR in this patient group, has been demonstrated in a small number of previous studies, however, the time to CMR varied widely and sample

sizes were small. (7-11) This may explain the disparate diagnostic yield of CMR in the literature, ranging from as low as 30% to as high as 90%. (29,30,32–34,36,37) The variation in the diagnostic yield in the literature is also explained by not having performed a comprehensive CMR image acquisition protocol including images for myocardial oedema. (36)

The patho-physiology of myocarditis and cardiomyopathy is well understood, but the concept is slightly unclear in MI with unobstructed coronaries. Several mechanisms have been proposed to explain this. Firstly, these patients may have a small branch artery occlusion that was missed by angiography. Secondly, there may be spontaneous recanalization where no intracoronary lesions can be detected after plaque rupture. Other mechanisms include an embolic event and coronary vasospasm.(160) Thus, it is important to conduct CMR on these types of patients where coronary angiography is unable to reveal the underlying patho-physiology.

In our cohort, the most common diagnosis was myocarditis (n=54), followed by MI (n=53). These findings are similar to other studies revealing myocarditis and MI to be the two most common diagnoses. (10-15) However, literature suggests myocarditis to be slightly more common than MI (10-13,15), contrary to our study where myocarditis and MI had similar prevalence. In our study we used established criteria (Lake Louise Criteria) for diagnosing myocarditis(55), whereas other studies do not mention the use of these criteria.(10-15)

In most studies patients have been imaged in a 1.5T system while in a couple of studies 3T scanner was used. (34)(32) Although 3T has increased signal strength, it is unlikely that the CMR diagnostic pick-up rate changes significantly between the 2 MRI systems. The studies by Leurent G et al and Chopard R et al have both imaged their patients in a 3T system and overall diagnostic rate was not different compared to the other studies. (34)(32)

Our study included the largest patient number; furthermore, STIR T2-imaging and early gadolinium enhancement sequences were consistently used in every patient unlike other studies (36)(33), suggesting our results to be more reliable and robust.

Our study demonstrates the importance of performing CMR to maximize the diagnostic ability of this test to identify a final diagnosis. Imaging patients ≤ 2 weeks from acute presentation gives a window of opportunity to image the pathophysiological process before healing occurs. This applies in particular to myocarditis and Tako-Tsubo cardiomyopathy whose natural history includes myocardial oedema and inflammation in the acute phase, which usually resolves within a few weeks. (161,162)

Myocarditis may be difficult to diagnose clinically as there can be either no specific symptoms at initial presentation or symptoms resembling those of an acute MI.(163) Although myocardial biopsy is the gold-standard for diagnosis (53) this is rarely

performed. A recent consensus paper has recognized the increasing role of CMR in patients with suspected myocarditis, particularly in those presenting as ACS. (53)

Myocardial damage and oedema associated with myocarditis (55) and transient apical ballooning/Tako-Tsubo cardiomyopathy (61,164) are acute processes that may have a poor prognosis. (33)(165)(81,82) CMR can delineate the severity of myocarditis and Tako-Tsubo cardiomyopathy thereby guiding management and risk stratification. LGE is the best independent predictor of mortality in biopsy-proven viral myocarditis (70) and is better than the traditional markers like LV ejection fraction, LV end diastolic volume and NYHA symptom class. Moreover, normal CMR in patients with clinically suspected myocarditis, is associated with a good prognosis. (71) Prompt CMR diagnosis of an aggressive myocarditis may lead to the initiation of appropriate therapy, including immunosuppressant, early referral for myocardial biopsy or help in MR guided biopsy. Likewise, Tako-Tsubo cardiomyopathy is usually considered to be a benign reversible condition, however its arrhythmic risk is increasingly recognized. There are promising new CMR analyses which may help in risk stratification. (81) Identification of a reversible cardiomyopathy may help to prevent subsequent unnecessary invasive procedure (for example ICD implantation). Moreover CMR can also help in diagnosis and risk stratification in MI. CMR allow accurate assessment of infarct size (LGE), myocardial salvage and microvascular obstruction. All these high-risk features can only be delineated in the acute phase. Hence the rational of performing CMR early (≤ 2 weeks of acute presentation) to possibly prevent a misdiagnosis, thus guiding appropriate medical management.

CMR is a costly imaging modality, but it may reduce long-term costs; for example, length of hospital stay, unnecessary use of secondary prevention medication in non MI, performance or avoidance of subsequent invasive procedure as well as reducing follow-up clinic visits and further hospital admissions. Furthermore, CMR prevents false labelling of acute MI to patients who have a different diagnosis thereby having a huge impact on insurance, employment, and possibly in the quality of life of these patients.

4.1.5 Limitations

The timing of individual CMR scans was partly based on the referring physician's discretion or availability of CMR scan slot. However with propensity scoring analysis we have tried to match the early CMR cohort with the late CMR group thereby reducing the selection bias. Patient follow-up was not performed to look at the prognosis, especially to see whether normal CMR patients had a better prognosis. Although this is the largest study to have been conducted so far, the sample size is still limited in number; therefore a much larger multi-centre trial would be beneficial.

4.1.6 Conclusion

In this large cohort of patients with troponin positive chest pain but unobstructed coronary arteries studied with CMR, overall CMR identified a diagnosis in the majority (70%) of our patients, the most common diagnoses being myocarditis and

MI, followed by cardiomyopathy. The diagnostic value of CMR improved significantly when carried out within 2 weeks from presentation.

4.1.7 Future implication

- Clinical relevance: MINOCA is not uncommon
- Current ESC guidelines do not clearly address the management of ACS with unobstructed coronaries
- Our study has hinted on the improved diagnostic role of early CMR and
- Multicentre prospective randomised trial is warranted to confirm these results

The work presented in this chapter has been published in the following research article. I was the first author in the paper with Dr Chiara Bucciarelli-Ducci as the senior author: (166)

Dastidar AG, Rodrigues JCL, Johnson T et al. Myocardial Infarction with non-obstructed coronary artery: Impact of CMR early after presentation. JACC Cardiovasc Imaging 2017 Oct;10:1204-1206

I presented the abstract of the work at European Society of Cardiology Conference London 2015 and won the **Best Poster Abstract Award**.

4.2 Clinical Impact of CMR in MINOCA

4.2.1 Introduction

7-15% of patients with acute coronary syndrome(ACS) have non-obstructed coronary arteries, an entity known as myocardial infarction(MI) with non-obstructed coronary arteries(MINOCA).(153) In these patients, cardiac magnetic resonance(CMR) can identify different underlying aetiologies(160). However, the the impact of CMR on the clinical management are unknown. We aimed to evaluate the decision making implications of CMR in MINOCA.

4.2.2 Methods

204 consecutive patients (56±17yrs, 51%male) with troponin positive ACS(as per the ESC ST-elevation or Non-STE-ACS guidelines and 3rd Universal definition of MI) and unobstructed coronary arteries(MINOCA) with unclear final diagnosis, referred for CMR were included(September 2011-July 2014). 19% presented with ST-elevation on the ECG and the rest as non-STEMI. The mean troponin was 640ng/L(normal <14ng/L). The study was reviewed and approved by local Institutional Review Board. 1.5T CMR was performed using a comprehensive protocol (cines, T2-weighted, and late gadolinium enhancement, LGE sequences). Myocarditis was diagnosed using the Lake Louise Criteria, MI by territorial subendocardial/transmural LGE and Tako-Tsubo cardiomyopathy by modified Mayo Clinic criteria.

“Significant clinical impact” was defined as identification of a “new diagnosis” or “change in management”. For change in management we recorded: 1) changes in length of hospital stay (shorter/longer), 2) changes in discharge medications (introduction/discontinuation) or 3) introduction/avoidance of additional invasive procedures.

4.2.2.1 Impact of CMR on clinical management

“Post-CMR diagnosis” was also recorded and was subsequently compared to the “pre-CMR diagnosis” to investigate whether the results confirmed the “pre-CMR diagnosis” or identified a new diagnosis.

“Significant clinical impact” was defined as identification of a “new diagnosis” or “change in management”. For change in management we recorded: 1) changes in length of hospital stay (shorter/longer), 2) changes in discharge medications (introduction/discontinuation) or 3) introduction/avoidance of additional invasive procedures. Patients with both a new diagnosis and change in management were counted only once for measurement of significant clinical impact. Data on “significant clinical impact” was collected directly from medical records. Data was collected and interpreted by one of the primary investigators (cardiologists) in all cases. Another cardiologist, unaffiliated with the CMR, independently interpreted the data from all patients. This physician was blinded to the previous interpretations of “significant clinical impact.” A third independent cardiologist adjudicated any discrepancy between the interpreters.

4.2.2.2 Statistical analysis

To identify which clinical and CMR indices were associated with a “significant clinical impact”, we performed univariable (unadjusted) logistic regression analysis to estimate the unadjusted odds ratios (OR) and the 95% confidence intervals (CIs) for the following variables: age, sex, troponin T, indexed LV end-diastolic volume, LV ejection fraction, regional wall motion abnormality, myocardial oedema on T2 weighted imaging, and LGE. Multivariable stepwise regression was performed to identify the correlates of “significant clinical impact”.

Propensity matching was performed to minimise any selection bias due to the differences in clinical characteristics between early and late CMR groups. For each patient in the cohort, a propensity score indicating the likelihood of an early CMR was calculated by the use of a non-parsimonious multivariable logistic regression model. Covariates included in the logistic regression model to calculate the propensity score were age, gender, family history of ischaemic heart disease (IHD), diabetes mellitus, smoking status, hypertension, presentation (NSTEMI or STEMI), troponin T level and LV systolic function. To identify matched pairs of patients undergoing early or late CMR, a 1:1 optimal match with a ± 0.26 caliper and no replacement was used.

SPSS Version 23 (IBM Corp, Armonk, NY) was used for statistical analysis. Probability values were two-sided, and values of $p < 0.05$ were considered significant.

4.2.3 Results

Overall, CMR provided a final diagnosis in 70%(n=143) of patient (Myocarditis 27%, and closely followed by MI 26%)

4.2.3.1 Significant clinical impact

Overall the findings of the CMR led to significant clinical impact in nearly two-thirds of cases (66%), which included a new diagnosis in 54% of cases and a change in management in 41% of cases (Figure 4-1). A total of 29% of patients had both a new diagnosis and a change in management. In 54% a completely new diagnosis emerged as a result of CMR compared to the baseline diagnosis derived from demographic, cardiac risk factors, ECG, echocardiogram, coronary angiogram and cardiac biomarker assessment. CMR results directly led to performance of subsequent invasive procedures (for e.g. myocardial biopsy, ICD implant, ventricular assist device etc) in 5% or avoidance (for e.g. myocardial biopsy, ICD implant, etc) in 4%.

Diagnosis ↑	New Diagnosis	25%	29%
	No Change	34%	12%
	Clinical Impact Overall (n = 204)	No Change	Change in Management
		Management →	

Figure 4-1 Overall clinical impact (n = 204). White cells denote no change, green cells show if there was a new diagnosis or a change in management, and pink cells show if both were present.

CMR changed the individual pre-CMR diagnosis to a new diagnosis in more than half of the cases. The next table shows the comparison of pre-CMR diagnosis with post-CMR diagnosis. **Table 4-2**

Table 4-2 Comparison of pre-cardiac magnetic resonance (CMR) with post-CMR diagnosis. Green cells denote changes in diagnosis, pink cells show an agreement between pre- and post-CMR, and white cells show if the CMR showed a structurally normal heart. Uncertain was defined when the referring clinician had ≥ 2 differential pre-CMR diagnoses. CM = cardiomyopathy; MI = myocardial infarction; MINOCA = myocardial infarction with nonobstructed coronary arteries.

		Post-CMR Diagnosis				
Pre-CMR Diagnosis	Total Sample n = 204	Myocarditis	MI	TakoTsubo	Other CM	Normal CMR
	Myocarditis	34	23	5	4	7
	MI	10	6	8	6	1
	TakoTsubo	1	5	3	0	2
	Other CM	1	0	1	0	0
	Uncertain	8	19	2	8	50

4.2.3.2 Propensity score matched cohort

Propensity score matching identified 58 pairs of early and late subjects. Baseline characteristics are summarized in Table 4-1. The results confirmed the significantly higher diagnostic yield in the “early” vs “late” CMR propensity matched group (88% vs 50% $p < 0.0001$). Myocarditis (33%) was the most common diagnosis in the “early” group, whereas MI (22%) was most prevalent in the matched “late” group. The prevalence of MI was not different in the “early” and “late group (22% vs 26% respectively, $p = 0.83$).

The clinical impact also improved significantly in the “early” CMR group compared to the propensity score matched “late” group (76% vs 51%, $p=0.01$).

4.2.3.3 Predictor of significant clinical impact

Age (OR 1.024, 95% CI 1.006-1.041, $p=0.008$), myocardial oedema (OR 1.765, 95% CI 0.938-3.323, $p=0.078$) and LGE (OR 2.393, 95% CI 1.318-4.345, $p=0.004$) were significant univariable predictors of significant clinical impact ($p<0.1$ considered significant for univariate analysis). In a multivariable model adjusting for clinical and imaging parameters, only age (OR 1.035, 95% CI 1.013-1.058, $p=0.002$) and LGE (OR 2.411, 95% CI 1.17-4.968, $p=0.017$) remained significant. Table 4-3.

Table 4-3 Predictors of clinical impact –univariate and multivariate logistic regression analysis

Univariate analysis					Multivariate analysis			
Variables	Sig.	OR	95% CI		Sig.	OR	95% CI	
			Lower	Upper			Lower	Upper
Age	0.008	1.024	1.006	1.041	0.002	1.035	1.013	1.058
Sex	0.77	1.091	0.609	1.954	0.604	0.831	0.413	1.673
Troponin	0.209	1	1	1.001	0.474	1	1	1.001
STEMI	0.224	1.63	0.742	3.577	0.966	0.981	0.412	2.338
iEDV	0.291	1.006	0.995	1.017	0.316	1.006	0.994	1.019
LVEF	0.597	0.995	0.975	1.015	0.847	1.002	0.98	1.025
RWMA	0.121	1.616	0.881	2.966	0.959	1.02	0.475	2.192
Oedema	0.078	1.765	0.938	3.323	0.527	1.298	0.579	2.912
LGE	0.004	2.393	1.318	4.345	0.017	2.411	1.17	4.968

LVEF – left ventricular ejection fraction, iEDV – indexed end diastolic volume, RWMA- regional wall motion abnormality & LGE – late gadolinium enhancement

4.2.4 Discussion

Despite the clinical utility of peak cardiac biomarkers and LV function in determining patient diagnosis, our study has shown that only LGE was a significant predictor of clinical impact out of all the investigation parameters thereby emphasising on the role of advanced tissue characterisation beyond conventional echocardiogram.

CMR is a costly imaging modality, but it may reduce long-term costs; for example, length of hospital stay, unnecessary use of secondary prevention medication in non MI, performance or avoidance of subsequent invasive procedure as well as reducing follow-up clinic visits and further hospital admissions. Furthermore, CMR prevents false labelling of acute MI to patients who have a different diagnosis thereby having a huge impact on insurance, employment, and possibly in the quality of life of these patients. In our study, CMR had a clinical impact in more than 2/3rd of patients, which improved significantly with the timing of CMR. Thus, we would advocate widespread adoption of early (≤ 2 weeks) CMR in all ACS patients with unobstructed coronaries, to facilitate appropriate diagnosis and future treatment.

4.2.5 Limitations

The timing of individual CMR scans was partly based on the referring physician's discretion or availability of CMR scan slot. However, with propensity scoring analysis we have tried to match the early CMR cohort with the late CMR group thereby reducing the selection bias. Patient follow-up was not performed to look at the prognosis, especially to see whether normal CMR patients had a better prognosis. Although this is the largest study to have been conducted so far, the sample size is still limited in number; therefore a much larger multi-centre trial would be beneficial.

4.2.6 Conclusion

CMR made a significant additive clinical impact on management and/or diagnosis in 66% of patients, with LGE being the best independent predictor of impact. Moreover, the clinical impact of CMR improved significantly when carried out within 2 weeks from presentation.

4.2.7 Future implication

- Clinical relevance: MINOCA is not uncommon
- Current ESC guidelines do not clearly address the management of MINOCA
- Our study for the first time has hinted on the clinical impact of CMR on subsequent management
- Multicentre prospective randomised trial is warranted to confirm these results

The work presented in this chapter has been published in the following research article. I was the first author in the paper with Dr Chiara Bucciarelli-Ducci as the senior author: (166)

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I presented the abstract of the work at European Society of Cardiology Conference London 2015 and won the **Best Poster Abstract Award**.

4.3 Prognostic impact of CMR and traditional risk markers

4.3.1 Introduction

Acute coronary syndrome (ACS) is one of the leading causes of mortality and morbidity worldwide.(152) Definite diagnosis of ACS is crucial for ensuring appropriate patient management. As per the international guidelines, patients presenting with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation-acute coronary syndrome (NSTEMI/ACS) proceed to immediate or inpatient coronary angiography, respectively, with the aim to identify and treat a culprit coronary artery occlusion or stenosis.(5,8) However, in 7-15% of these patients no significant coronary obstruction is identified, thus being classified as MINOCA (Myocardial infarction with non-obstructive coronary arteries).(8) MINOCA represents a diagnostic dilemma, with subsequent uncertain clinical management. A recent registry study has shown beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on outcome in patients with MINOCA.(167)

The underlying pathophysiological mechanisms occurring in MINOCA are complex and multifactorial. A recent review article by Niccoli et al. described the potential mechanisms and proposed a management algorithm for this cohort.(153) Patients with MINOCA are thought to have a better prognosis, and consequently do not receive appropriate secondary prevention medications.(22) However, recent studies suggest that all-cause mortality may be as high as 4.7% at 12 months.(21,28) The latest ESC guidelines on the management of STEMI has included MINOCA suggesting

a potential role for cardiovascular magnetic resonance (CMR) in this cohort.(8) Confirmation or exclusion of myocardial infarction (MI) by (CMR) facilitates tailoring of medical therapy, ensuring appropriate long-term secondary prevention and modification of risk but also minimizing exposure to anti-platelet therapy and the associated bleeding risks for those with a non-coronary aetiology for the MINOCA presentation.(160) CMR also helps in reassuring the patient by having identified a clear cause of the episode that led to their admission to hospital. Few previous studies have shown that CMR can identify the underlying diagnosis, most commonly: acute/chronic myocarditis, acute MI with spontaneous recanalization/embolus, stress cardiomyopathy (Takotsubo) or other cardiomyopathies.(29,30,32–34,36,37) Only in a small proportion of cases, no abnormality is identified by CMR. The variable proportion of normal cases in the different studies may be due to the time delay between the acute presentation and CMR, (168) suggesting that the time between acute presentation and CMR can play a role in identifying the early reversible abnormalities that may resolve when patients are scanned later. Recent studies have demonstrated the prognosis in the individual diagnostic categories like myocarditis and Takotsubo cardiomyopathy. (169–171) However, there is no evidence in the literature on the prognostic significance of the CMR findings and conventional risk factors in MINOCA. The only study which looked at mid-term mortality was by Mittal et al. (172) However they looked at patients presenting via the primary percutaneous coronary angiography pathway with non-obstructed coronaries. 60% of the study population had normal troponin thereby not strictly MINOCA. Our study aims to assess the prognostic impact of CMR and conventional risk factors in patients with MINOCA.

4.3.2 Methods

4.3.2.1 Study population

In this longitudinal observational study, consecutive patients presenting with MINOCA (chest pain, elevated troponin and non-obstructed coronary arteries) as per the new ESC STEMI Guideline(8) and undergoing CMR were included and followed up prospectively. Fig 1. We excluded patients admitted with suspected heart failure or arrhythmic events at presentation. The study was performed at a large cardiothoracic tertiary centre in the South-West of England; data were collected on consecutive patients scanned from September 2011 to December 2015. Patients were identified either presenting with STEMI or NSTEMI. Non-obstructed coronaries were defined as: TIMI III flow; <50% stenosis in any coronary artery.(8) Troponin T level <14ng/L was considered normal. 'False positive' troponin possibilities: a single troponin elevation (<5x upper limit of normal), which was not repeated during the admission or if a single elevated troponin was followed by a second normal troponin level within 24 h were excluded from study. (5) **Figure 4-2**

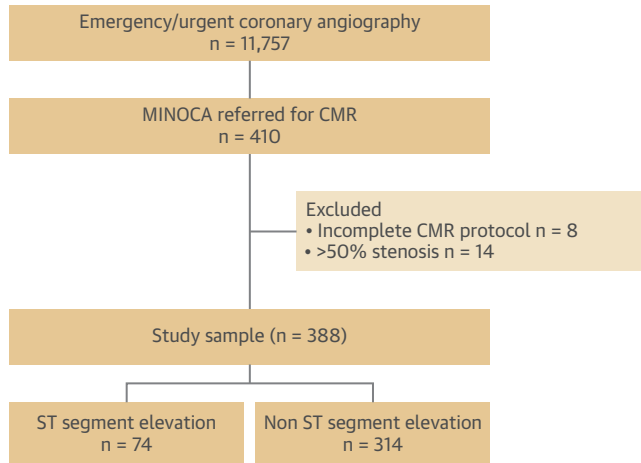


Figure 4-2 Study flow-chart

The study was reviewed and approved by the local Institutional Review Board.

4.3.2.2 CMR protocol

CMR was performed at 1.5T (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). A comprehensive CMR protocol was carried out including cine, myocardial oedema and myocardial scarring imaging. In particular, cine images were performed using a steady-state free-precession sequence acquired in three long axis planes and a stack of short axis images covering the left ventricle (LV) and T2-weighted (T2-STIR) sequence images were acquired in the same planes as the cine images with standard parameters, as previously described.(41,148) Intravenous gadolinium-chelate contrast agent (gadobutrol) was administered at a dose of 0.1 mmol kg⁻¹ of body weight. Images were acquired 2-3min after contrast injection (early gadolinium), whilst late gadolinium enhancement (LGE) images were acquired 15-20minutes after contrast injection using a standard inversion recovery segmented

gradient echo sequence, as previously described. (41,148) Diffuse and focal myocardial oedema was analysed using both the early gadolinium and the T2-STIR images. Oedema was considered present when the ratio of signal intensity between the myocardium and the mean signal intensity of the skeletal muscle was >2 .

4.3.2.3 CMR analysis

All CMR studies were analysed and reported by a consultant with >12 years of CMR experience and with ESC CMR level 3 certification (CBD). Patients were grouped into 4 categories based on their CMR characteristics: myocardial infarction (MI) (embolic/spontaneous recanalization), myocarditis, cardiomyopathy and normal CMR. The latter corresponded to a structurally normal heart, defined as no regional wall motion abnormality (RWMA) (except for dyssynchrony secondary to bundle branch block), no myocardial oedema, and no myocardial LGE (scarring) (except non-specific LGE in LV/RV insertion points). Myocarditis was diagnosed based on fulfilling two out of three Lake Louise Criteria: STIR T2-weighted sequences detecting myocardial oedema; early gadolinium sequences detecting hyperaemia; epicardial or mid-myocardial LGE, as previously described (55). MI was diagnosed based on territorial subendocardial and/or transmural LGE. Takotsubo cardiomyopathy was diagnosed based on the STIR T2-weighted images detecting myocardial oedema and regional wall motion in the mid-cavity or apical distribution with no myocardial LGE, all in accordance with the modified Mayo Clinic criteria.(156) Dilated cardiomyopathy, hypertrophic cardiomyopathy and cardiac amyloidosis were

detected based on specific tissue characterization characteristics and were all grouped under cardiomyopathy together with Takotsubo cardiomyopathy.(29)

4.3.2.4 Study primary end-point

The end-point of the present study was all-cause mortality.

Patient related data were collected directly from medical records. Follow up was performed centrally by analyzing the mortality data obtained from the NHS summary care records. Data was collected and interpreted by one of the primary investigators in all cases.

4.3.2.5 Statistical analysis

Baseline patient characteristics, conventional risk markers and CMR findings are described according to the diagnostic groups. Data for continuous variables are presented in mean \pm standard deviation or medians as appropriate. Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables were compared using one-way analysis of variance with (ANOVA) with Bonferroni correction for multiple comparisons. Continuous variables that were not normally distributed were compared by Kruskal–Wallis tests. In univariate analyses the association of time variables to mortality was assessed using Kaplan–Meier curves and the log-rank test. Univariable and multivariable associations of risk covariates with mortality were assessed using Cox proportional hazard regression analyses. Only variables with a p value<0.05 in univariable

analyses were used in multivariable model. SPSS Version 23 (IBM Corp, Armonk, NY) was used for statistical analysis. Probability values were two-sided, and values of $p < 0.05$ were considered significant. Due to paucity of mortality data on the MINOCA subgroups post-hoc power calculation was performed based on the study findings.

4.3.3 Results

11757 patients underwent emergency or urgent coronary angiography during the recruitment period, out of which 410 patients with MINOCA underwent CMR assessment. 2% ($n=8$) were excluded due to incomplete protocol and 3% ($n=14$) due to coronary artery disease which were deemed $>50\%$ stenosis thereby leaving a study sample size of 388. CMR was able to identify a cause for the troponin rise in 74% of cases. Clinical characteristics of the overall population ($n=388$) and for separate patients' groups based on the CMR diagnosis are summarized in **Table 4-4**. There was a low prevalence of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking and family history), with no difference across the groups. The median time delay between acute presentation and CMR was 37 days. 37% of our patients underwent the scan within 2 weeks from presentation. In a median follow up of 1262 days (3.5 years), the overall all-cause mortality was 5.7%.

Table 4-4 Demographic characteristics.

	Total (n = 388)	MI (n = 97)	Myocarditis (n = 96)	CM (n = 96)	Normal (n = 99)	Global p Value
Age, yrs	56 ± 17	62 ± 12	42 ± 17	64 ± 12	54 ± 16	<0.001
Women	48	56	23	61	54	<0.001
Family history of IHD	3	2	4	1	3	0.57
Diabetes	6	8	5	6	4	0.64
Hypertension	13	16	9	14	14	0.54
History of smoking	7	4	5	10	7	0.32
BMI	26.5	27.3	26.5	25.7	26.4	0.18
Median troponin T, ng/l	497	660	924	419	202	0.03
Presentation as STEMI	19	19	19	25	14	0.29
Median interval, days (presentation and CMR)	37	37	21	12	47	<0.001
Median follow-up, days	1,262	1,246	1,336	1,231	1,276	0.09
All-cause mortality	6 (22)	4 (4)	2 (2)	15 (14)	2 (2)	<0.001

4.3.3.1 Conventional risk factors

Age: The mean age of the total population was 56±17years.

Kaplan-Meier curves were drawn showing the risk of mortality according to the different age categories (<40years, 40-59years, 60-79years and >79years). There was a strong association between increasing age and mortality (Log rank 23.2, p<0.001)

Figure 4-3

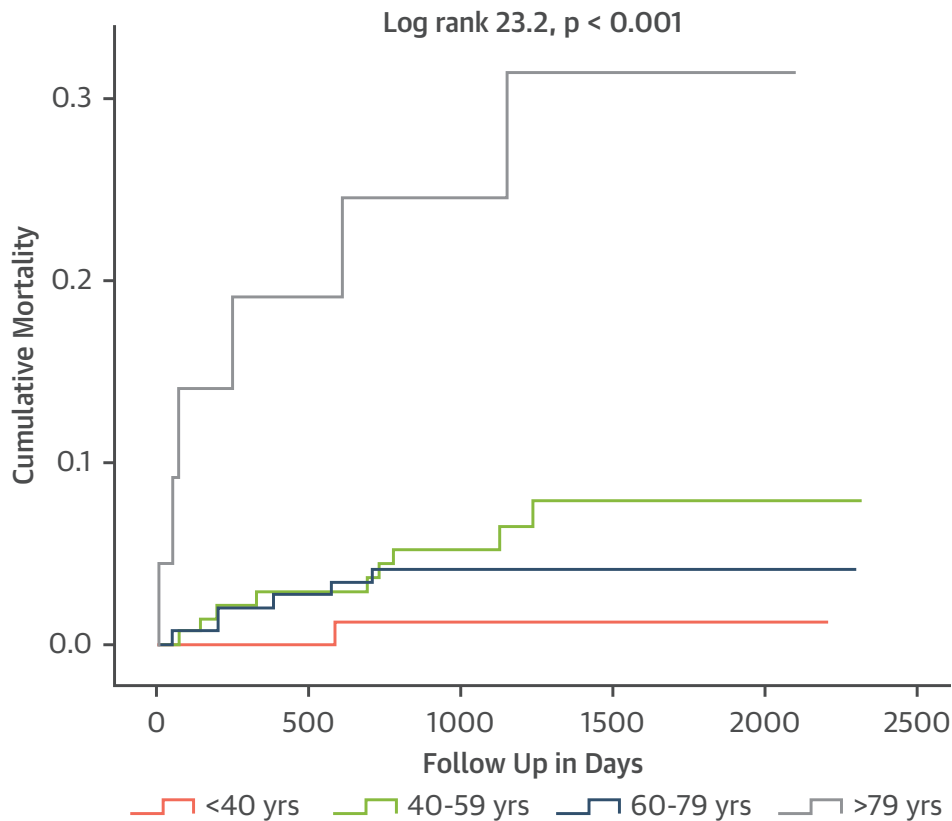


Figure 4-3 Age as a marker of mortality. Kaplan-Meier curves showing the risk of mortality according to age group.

Gender: 48% of the total cohort was female. 98% of the patients diagnosed with Takotsubo cardiomyopathy were female. There was no significant association between gender and mortality in the overall cohort (log rank 2.5, $p=0.1$).

Troponin T: The median troponin T for the entire cohort was 497ng/L. The median troponin T level in the different groups: MI, myocarditis, cardiomyopathy and the normal cohort were 660ng/L, 924ng/L, 419ng/L and 202ng/L, respectively (Kruskal-Wallis, $p<0.001$).

ECG at presentation (STEMI or NSTEMI): 19% of our study population presented with ST-segment elevation on the 12-lead ECG and the other 81% as NTE-ACS.

Kaplan-Meier curves were drawn showing the risk of mortality according to the ECG presentation as ST-elevation or no ST-elevation. There was a strong association between presentation as ST-elevation and mortality (log rank 7.4, $p=0.007$). **Figure 4-**

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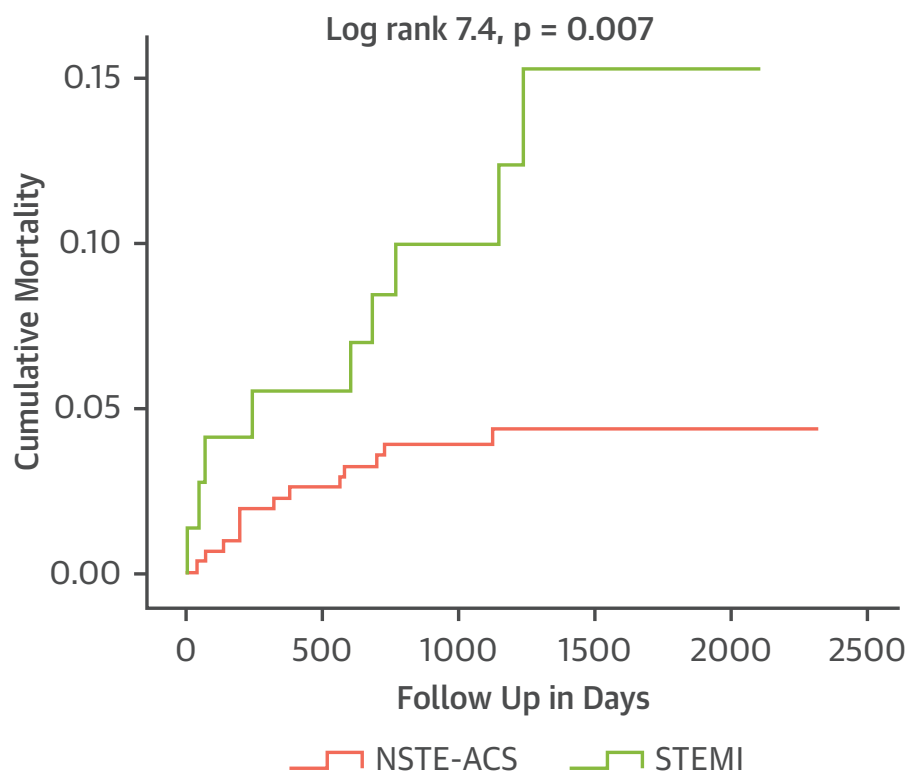


Figure 4-4 ECG at presentation. Kaplan-Meier curves showing the risk of mortality according to presence or absence of ST segment elevation on the presenting ECG

4.3.3.2 CMR characteristics and diagnosis

The CMR characteristics are described according to the diagnosis groups. **Table 4-5**

Table 4-5 CMR characteristics of the different diagnostic categories

	Total (n = 388)	MI (n = 97)	Myocarditis (n = 96)	CM (n = 96)	Normal (n = 99)	Global p Value
iEDV, ml/m ²	81	78	83	90	74	<0.001
iESV, ml/m ²	34	30	32	47	26	<0.001
iSV, ml/m ²	47	48	50	43	48	<0.001
LVEF	61	63	62	52	67	<0.001
iLV mass, g/m ²	66	63	67	75	59	<0.001
RWMA	39	59	31	59	6	<0.001
LGE	58	100	94	34	6	<0.001
No. of LGE segments	1 (0-2)	1 (1-2)	3 (2-4)	0 (0-1)	0	<0.01
Myocardial edema, %	34	52	52	34	0	<0.001
No. of edema segments	0 (0-2)	1 (0-2)	2 (0-4)	0 (0-5)	0	<0.01

MI was the most prevalent diagnosis (25%, 97/388 patients), followed by myocarditis (25%, 96/388) and cardiomyopathy 25%, whilst 26% had a structurally normal heart and were grouped into the 'normal CMR' category.

LV volumes: In the overall cohort the mean indexed end-diastolic volume (iEDV) was 81ml/m². On Bonferroni correction the iEDV in the cardiomyopathy was significantly higher than MI and normal CMR category.

The mean indexed end-systolic volume (iESV) and indexed stroke volume (iSV) in the overall cohort were 34ml/m² and 47ml/m², respectively.

LV ejection fraction: The mean LV ejection fraction for the whole cohort was 61%.

On Bonferroni correction the LVEF in the cardiomyopathy was significantly lower than MI, myocarditis and normal CMR category. In addition the LVEF in the myocarditis was significantly lower than normal CMR category.

Regional wall motion abnormalities: Overall 39% of patients had RWMA. The prevalence of RWMA in the different diagnostic categories MI, myocarditis, cardiomyopathy and normal were 59%, 32%, 60% and 6% respectively (p<0.001). The normal CMR category had RWMA secondary to bundle branch block on ECG.

Myocardial oedema: The overall prevalence of focal myocardial oedema was 34% based on T2 STIR and/ or early gadolinium enhancement. Focal myocardial oedema was absent in the patients with normal CMR. Additional analysis of the normal CMR cohort revealed no evidence of diffuse myocardial injury in any of the patients. The prevalence of myocardial oedema among MI, myocarditis and cardiomyopathy groups were 52%, 52% and 33% respectively (p<0.001).

Late Gadolinium Enhancement: LGE was present in 58% of the entire cohort.

It was present in all cases of MI (subendocardial and/ or transmural LGE) and 94% of myocarditis (mid-wall and/or epicardial LGE). Only 34% of the cardiomyopathy group had LGE. 6% of patients with normal CMR had evidence of LGE only in the LV/RV insertion points, currently considered a non-specific finding.

4.3.3.3 Cardiomyopathy subgroup analysis

In the cardiomyopathy group, 43% had Takotsubo cardiomyopathy, 29% dilated cardiomyopathy and 18% hypertrophic cardiomyopathy. The remaining comprised of infiltrative cardiomyopathy (amyloidosis)(n=4), hypertensive heart disease(n=4) and valvular heart disease(n=2) and were grouped as 'other'. There was no statistically significant difference in the mean age and presentation as STEMI, however there was a significant difference in the gender among the different cardiomyopathy subgroups. There was a significant difference in the CMR parameters among the different cardiomyopathy subgroups. **Table 4-6**

Table 4-6 Characteristics of the cardiomyopathy subgroups

	TCM (n = 41)	DCM (n = 28)	HCM (n = 17)	Others (n = 10)	Global p Value
Age, yrs	68 ± 10	63 ± 13	60 ± 17	60 ± 12	0.05
Women	98	32	47	33	<0.001
STEMI	38	18	24	0	0.07
iEDV, ml/m ²	77	128	67	81	<0.001
iESV, ml/m ²	35	87	20	36	<0.001
iSV, ml/m ²	42	41	48	44	0.298
LVEF	56	33	70	59	<0.001
iLV mass, g/m ²	61	85	87	88	<0.001
Mortality	6	5	0	3	<0.01

4.3.3.4 Treatment prior to CMR

The use of Aspirin, Other antiplatelet, ACE-Inhibitor/Angiotensin Receptor blocker, Beta-blocker and Statin use in the overall cohort was 93%, 61%, 66%, 65% and 57% respectively. There was no significant difference in the use of medications among the different diagnostic categories. **Table 4-7.**

Table 4-7 Treatment prior to CMR

Pre-CMR Treatment	MI (n = 97)	Myocarditis (n = 96)	CM (n = 96)	Normal (n = 99)	Global p Value
Aspirin	95	92	91	92	0.81
Other antiplatelet	61	59	60	63	0.31
ACE inhibitor/ARB	65	66	69	66	0.92
Beta-blocker	65	64	71	62	0.58
Statin	62	53	59	56	0.66

4.3.3.5 Prognosis in different CMR categories

In a median follow up of 1262days(3.5years), the overall all-cause mortality was 5.7% with worst prognosis identified in the cardiomyopathy group (15% mortality). The mortality rate in the different groups was: cardiomyopathy 15%, MI group 4%, myocarditis group 2%, and the normal group 2% ($p=0.001$).

Kaplan-Meier curves were drawn showing the risk of mortality according to the different CMR diagnosis, showing a strong association between CMR categories and mortality (log rank 19.9, $p<0.001$). **Figure 4-5**

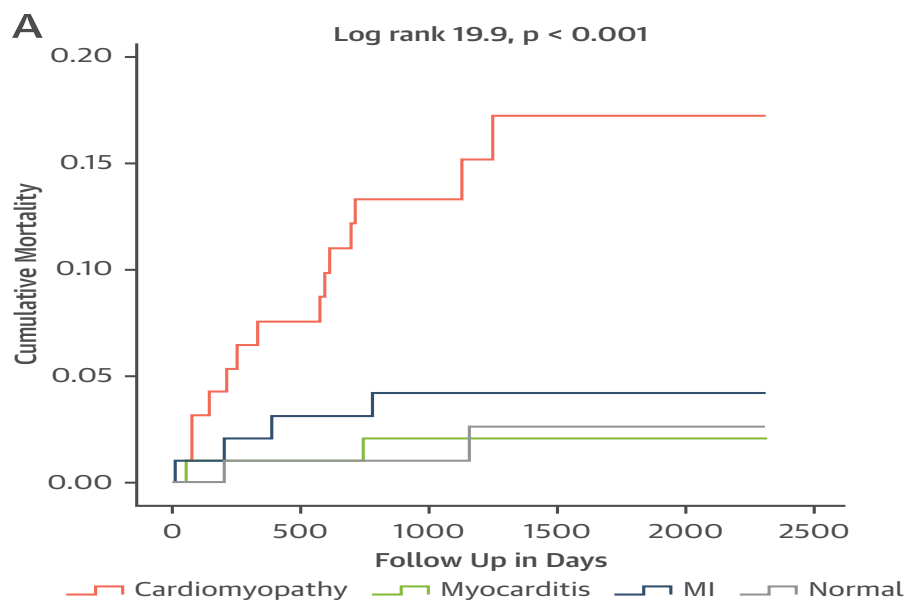


Figure 4-5 Cumulative Mortality According to CMR diagnosis.

Kaplan-Meier curves showing the risk of mortality according to CMR diagnosis (MI vs Myocarditis vs Cardiomyopathy vs normal),

An additional Kaplan-Meier curve was drawn for Takotsubo cardiomyopathy, showing a significantly higher mortality in Takotsubo group compared to any other diagnosis (log rank 7.3, $p=0.011$). **Figure 4-6**

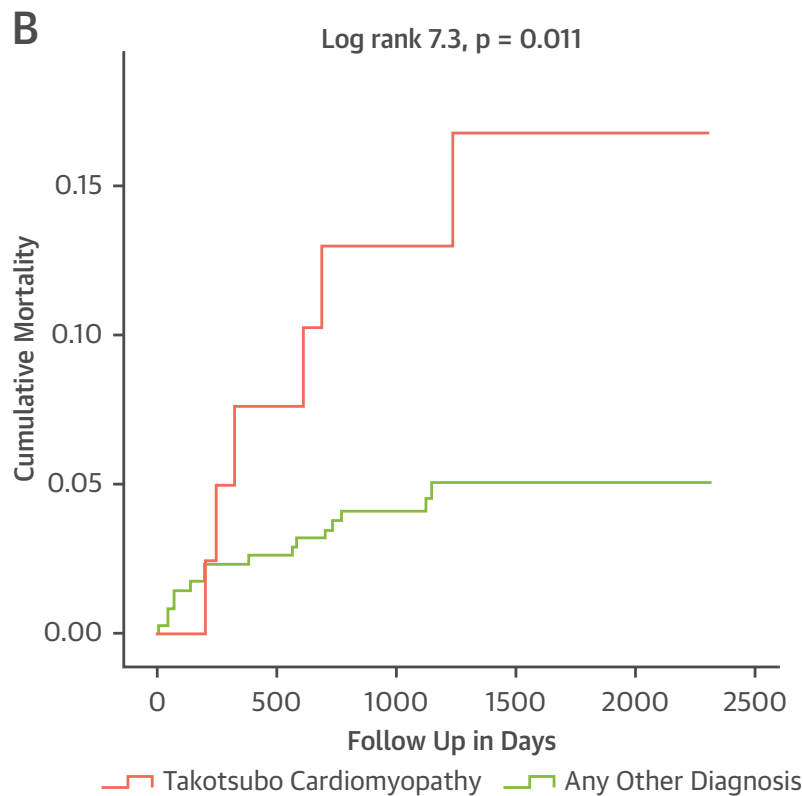


Figure 4-6 Comparing cumulative mortality in takotsubo vs any other diagnosis

Kaplan-Meier curves showing the risk of mortality according to CMR diagnosis of Takotsubo cardiomyopathy vs any other diagnosis

4.3.3.6 Predictors of all cause mortality

Age, presentation with ST-elevation on ECG, iEDV, log troponin, LV ejection fraction and CMR diagnosis of cardiomyopathy were significant univariable predictors of mortality ($p < 0.05$ considered significant for univariate analysis). In a multivariable model only CMR diagnosis of cardiomyopathy (hazard ratio 3.0, 95% CI 1.08-8.37,

p=0.034) and presentation with ST-elevation (hazard ratio 3.1, 95% CI 1.27-7.68, p=0.013) remained significant. **Table 4-8.**

Table 4-8 Predictors of mortality –univariate and multivariate logistic regression analysis

	Univariate Analysis				Multivariate Analysis			
	Significance	HR	95% CI		Significance	HR	95% CI	
			Lower	Upper			Lower	Upper
Age group	0.008	2.046	1.203	3.48	0.100	1.645	0.908	2.978
Sex	0.302	1.564	0.669	3.659				
BMI	0.484	0.968	0.884	1.06				
Log-peak troponin	0.041	0.509	0.267	0.971	0.094	0.565	0.290	1.101
STEMI	0.01	3.059	1.307	7.157	0.013	3.125	1.271	7.684
iEDV	0.008	1.016	1.004	1.028	0.258	1.01	0.993	1.028
LVEF	0.001	0.958	0.936	0.981	0.851	0.996	0.96	1.034
RWMA	0.132	1.905	0.823	4.41				
LGE	0.161	0.544	0.233	1.274				
Edema	0.228	0.542	0.20	1.469				
MI	0.472	0.672	0.227	1.986				
Myocarditis	0.098	0.293	0.068	1.253				
CM	0.001	5.628	2.361	13.417	0.034	3.013	1.084	8.373
Normal	0.091	0.285	0.067	1.219				

4.3.3.7 Mortality risk markers (ST-elevation on presentation ECG + CMR diagnosis)

A risk assessment tool for predicting mortality was constructed on the basis of the 2 variables: CMR diagnosis of cardiomyopathy and presentation with ST-elevation on ECG. A first group was defined as 242 patients with any other CMR diagnosis except cardiomyopathy and presentation as NSTEMI-ACS. A second group was made up of 122 patients with only one of the factors altered i.e. either a CMR diagnosis of cardiomyopathy or presentation with ST-elevation on ECG. Finally, the third group

included 24 patients with CMR diagnosis of cardiomyopathy and presentation with ST-elevation on ECG. The mortality rates in these 3 groups were (4/242) 1.6%, (13/122) 10.6%, and (5/24) 20.8%. respectively. Kaplan-Meier curves were drawn showing the risk of mortality in these 3 groups, showing a strong association between number of risk marker and mortality (log rank 23.6, $p < 0.001$). **Figure 4-7.**

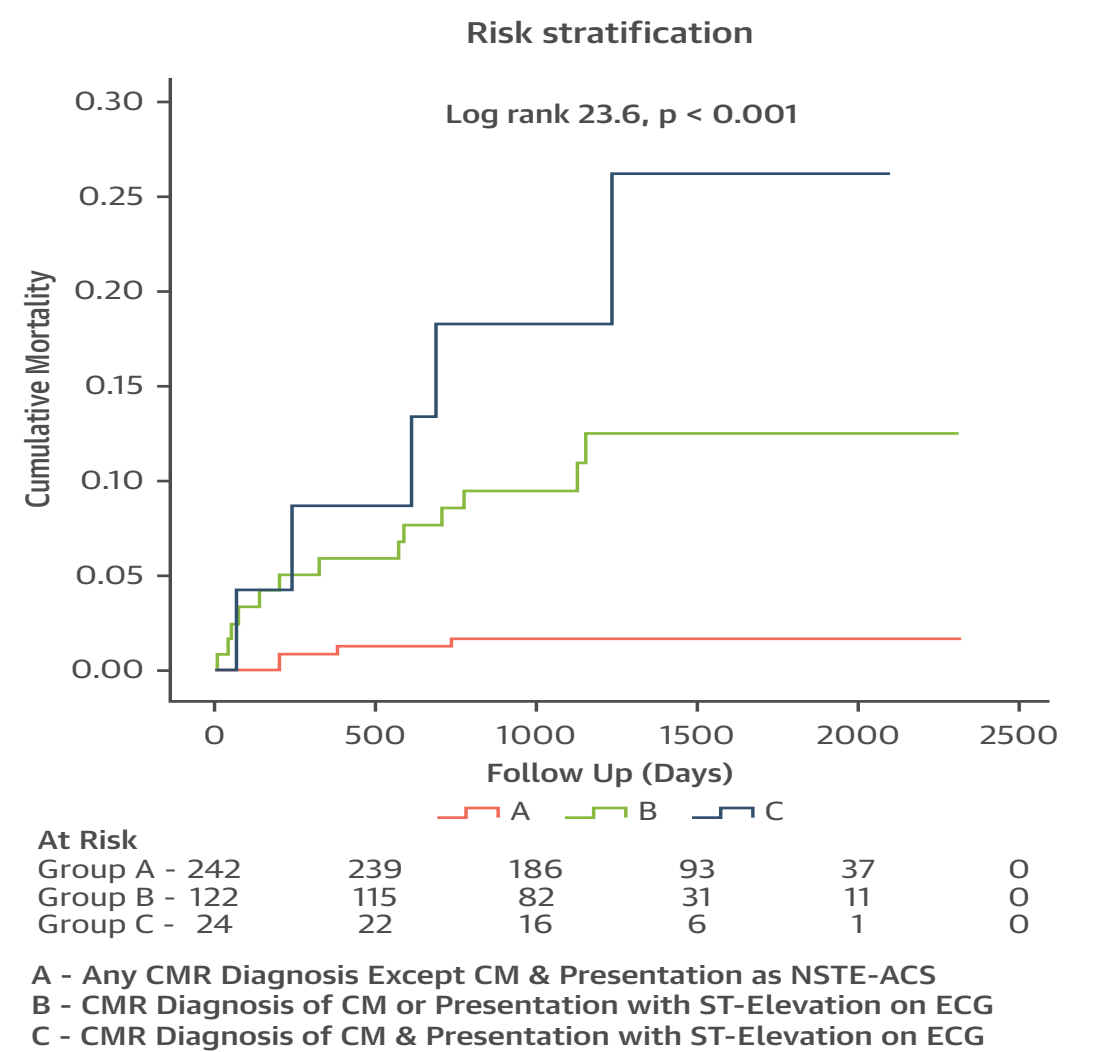


Figure 4-7Kaplan-Meier curves showing the risk of mortality according to risk score category (Score 0 - Any CMR diagnosis except cardiomyopathy & presentation as

**NSTE-ACS, Score 1- CMR diagnosis of cardiomyopathy or presentation as STEMI,
Score 2 - CMR diagnosis of cardiomyopathy & presentation as STEMI)**

4.3.4 Discussion

This is the largest to date cohort of MINOCA patients assessed with CMR, and the first study to assess the prognostic role of CMR and conventional risk factors in patients with MINOCA. The main findings are as follows: 1) CMR can identify a diagnosis in 3/4 patients presenting with MINOCA and suitable for CMR assessment, 2) CMR diagnosis of cardiomyopathy is the strongest CMR marker associated with mortality, 3) among the conventional risk markers, ECG presentation with ST-elevation is the most potent predictor of mortality and 4) a combined risk assessment tool using the 2 parameters (cardiomyopathy and presentation with ST-elevation) provides further risk stratification in these patients.

4.3.4.1 Diagnostic role of CMR in MINOCA

It is important to identify a cause for MINOCA in order to guide ongoing management and provide patient's guidance. As a non-invasive imaging technique, CMR is able to identify a diagnosis in these patients in up to 3/4 cases, irrespective of timing of scan. The diagnostic role of CMR in this patient group has been demonstrated in a small number of previous studies with smaller sample sizes. (7-11) However, the diagnostic yield of CMR in the literature was disparate, ranging from as low as 30% to as high as 90%. (29,30,32–34,36,37) The variation in the diagnostic

yield in the literature can be explained by the use of incomplete CMR protocol (edema imaging not always included) as well as the timing of the test , sometimes occurring several months after the acute event leading to the resolution of the reversible cardiac abnormalities. (36,168)

In our cohort, the most common diagnosis was MI (25%, n=97), closely followed by Myocarditis (25%, n=96) and cardiomyopathy (25%). However, the literature suggests myocarditis to be much more common than MI (10-13, 15), contrary to our result. The mean age in our study was much higher compared to the other studies on MINOCA which may have contributed to the higher prevalence of MI.(29,32) Another possible explanation could be the use of established criteria (Lake Louise Criteria) for diagnosing myocarditis(55), as well as an inclusion cut-off of <50% coronary artery stenosis.(10-15)

4.3.4.2 Prognostic role of CMR in MINOCA

Of all the CMR parameters examined (including LV size, LV function, LV mass, myocardial oedema, LGE and the overall CMR diagnosis), a CMR diagnosis of cardiomyopathy was associated with the worst prognosis (15% mortality). On a multivariable analysis involving both traditional markers and CMR characteristics, CMR-derived diagnosis of cardiomyopathy remained significant as an independent predictor of mortality.

Among the other CMR parameters assessed, LV ejection fraction and LV indexed end-diastolic volume were significant univariable predictors of mortality but not in multivariable analysis. These findings are particularly useful in justifying the role of CMR tissue characterization in MINOCA.

The cardiomyopathy group in our study was a heterogeneous group with Takotsubo cardiomyopathy being the most common (43% of the cardiomyopathy group). Takotsubo cardiomyopathy had the worst prognosis over a median follow up of 3.5 years (15% overall mortality) when compared to any other CMR diagnosis. The findings are comparable to the recent study by Templin et al. in which Takotsubo cardiomyopathy had a mortality of 5.6% per patient-year in long term follow up.⁽¹⁷¹⁾ CMR not only helps in diagnosis but it may also help in identifying the high risk Takotsubo cardiomyopathy cases by delineating the amount of myocardial oedema, RV involvement, thrombus, LV outflow tract obstruction. CMR derived apico-basal myocardial oedema gradient may be used as a marker of malignant arrhythmia risk.⁽⁸¹⁾

4.3.4.3 Conventional risk factors for prognosis assessment

Out of all the risk factors assessed, presentation with ST-elevation on ECG was an independent predictor of mortality. Age and log peak troponin were univariable predictors of mortality but not in multivariable analysis. Gender was not associated with mortality. The finding on peak troponin is particularly important as it is in contrary to the regular practice. High peak troponin level is often used as an arbitrary prognostic marker due to its evidence from acute coronary syndrome trials.

(173) The importance of the presentation ECG is a novel finding as it is often overlooked while managing patients with MINOCA.

4.3.4.4 Clinical implication

Our findings strengthen the evidence that CMR is a clinically relevant non-invasive imaging modality for the assessment of patients presenting with MINOCA. In a previous study we have demonstrated that CMR in MINOCA leads to a change in diagnosis in 54% and change in management in 41%. (17) The current study reinforces the impact of CMR, as a diagnosis of cardiomyopathy is associated with worst prognosis. Any other diagnosis except cardiomyopathy had a relatively low mortality (2-4%) thereby putting them in a good prognostic category.

This is the largest cohort to date to confirm the diagnostic role of CMR in patients with MINOCA and the first study looking at the prognostic role of CMR in this patient population.

Currently, there is no risk stratification algorithm for patients presenting with MINOCA. The results of our study suggest that ECG at presentation and CMR diagnosis might be useful predictors for risk stratification. This should be explored further and confirmed in larger multicenter studies.

4.3.5 Limitations

Several limitations merit consideration. This is a single centre study with relatively limited sample size. Although our study was designed to represent a real-world population, we potentially might have excluded higher-risk patients with contraindications to CMR (e.g., creatinine clearance <30 ml/min and intracardiac devices). However, our study included a broad range of consecutive MINOCA patients from a large catchment area, and only a limited number (2%) of patients were excluded from CMR. There may have been a referral bias as the study included MINOCA patients, referred for a CMR by the physician providing the care. However, our regular clinical practice at the Bristol Heart Institute includes CMR in patients presenting with MINOCA. The CMR was performed at a median of 37days from presentation and this may have impacted the diagnostic pick up rate as well as the prevalence of myocardial edema. Nevertheless, our study showed a significant prognostic impact irrespective of the timing of scan. Also, newer mapping techniques were not performed in this patients' cohort. The normal CMR group had few patients with bundle branch block and LGE in the insertion points which may not be classed as entirely normal, however the presence of diffuse myocardial injury was excluded on the basis of both the early gadolinium enhancement and T2 weighted images analysis. Lastly, myocardial biopsy was not carried out in these patients. However, well-established and clinically validated CMR criteria were used for the diagnosis of the individual cases.

4.3.6 Conclusion

In a large cohort of MINOCA, CMR (median 37days from presentation) established a diagnosis in almost 3/4 of cases. Among the conventional risk factors and CMR characteristics, ST-segment elevation on presentation ECG and CMR diagnosis of cardiomyopathy were independent predictors of mortality. Combined analysis of CMR diagnosis and ECG at presentation may allow robust stratification of patient outcomes.

4.3.7 COMPETENCY IN MEDICAL KNOWLEDGE:

CMR (median 37days from presentation) enabled in establishing a diagnosis in 74% of patients presenting with MINOCA. Patients presenting with ST-elevation on ECG and CMR diagnosis of cardiomyopathy have worst prognosis.

TRANSLATIONAL OUTLOOK:

- Clinical relevance: MINOCA is common and often represent a clinical dilemma
- Current ACC/ESC guidelines suggest some diagnostic tests but there is no recommended work up and management of MINOCA
- CMR is useful for both diagnosis and prognostication
- Large multicentre prospective trial is warranted to confirm these results and thereby enabling a tailored treatment strategy in this heterogeneous cohort

The work presented in this chapter has been published in the following research article. I was the first author in the paper with Dr Chiara Bucciarelli-Ducci as the senior author: (174)

Dastidar AG, Baritussio A, De Garate E et al. Prognostic role of cardiac MRI and conventional risk factors in Myocardial Infarction with non-obstructed coronary arteries. JACC Cardiovasc Imaging 2019 Feb (epub ahead of print)

I presented the abstract of the work at **European Society of Cardiology Conference** Barcelona 2017 and was the runner-up at the **Moderated Poster Presentation Competition**.

5 New CMR techniques in STEMI

5.1 Widespread tissue injury in STEMI and the impact of microvascular obstruction on widespread tissue injury

5.1.1 Introduction

Globally, ST-elevation myocardial infarction (STEMI) still remains one of the major medical emergencies, representing 30% of all acute coronary syndromes (ACS) admission to hospitals. (175) Even with successful and timely primary percutaneous coronary intervention, the mortality is significant for patients presenting with STEMI. The higher mortality rate in the higher-risk patients (176) justifies our continuous efforts to understand the pathophysiology of myocardial injury in order to improve the quality of care.

The myocardial tissue injury following STEMI in the culprit artery territory is characterized by a central infarct core surrounded by an area of myocardial oedema, which together constitute the area at risk. Cardiovascular Magnetic Resonance (CMR) can detect the myocardium at risk and myocardial salvage (area at risk minus infarct size) noninvasively. (41) T2 weighted CMR imaging sequence can delineate the area at risk, a zone of reversibly and irreversibly injured myocardium as validated against histological study.(177) Sometimes within the infarct core there are areas of microvascular obstruction(MVO) or intramyocardial hemorrhage(IMH), both of which are markers of poor prognosis(97,178). A post-mortem study of patients with STEMI demonstrated that myocardial tissue injury is not restricted to the territory

supplied by the culprit artery but it also affects the remote myocardium supplied by non-culprit arteries. (179) However, in that study presence of an active inflammatory infiltrate in unaffected viable myocardium following acute MI were shown via histological assessment of the autopsy specimen. This presents a limitation in delineating the findings in-vivo. Couple of recent CMR studies by Carrick et al and Bulluck et al. (180,181) has demonstrated inflammation of remote myocardium in STEMI by using T1 mapping technique. In both studies they have looked at the role remote myocardium native T1 in the acute phase in predicting outcome (eg adverse cardiovascular event or adverse cardiac remodeling). The aim of our study was to demonstrate in-vivo the presence of widespread myocardial changes including the remote myocardium in patients with AMI via advanced CMR myocardial tissue characterization (T1 and T2 mapping) without the need for gadolinium contrast. We also looked at the associates of increased remote myocardium injury like infarct size, presence of MVO.

5.1.2 Methods:

5.1.2.1 Study population

Thirty successfully reperfused STEMI patients (mean age 61 ± 10 years and 80% males) and 20 healthy volunteers were recruited. All patients were diagnosed with STEMI according to guidelines. (6,138) Exclusion criteria were: general contraindications to MRI, chronic atrial fibrillation, renal impairment with eGFR <30 , cardiogenic shock. This study was approved by the local ethics committee. All patients gave informed written consent. The acute STEMI patients were recruited to the Myocardial Oedema

in ST Segment Elevation Myocardial Infarction study NCT 01897350

(www.clinicaltrials.gov).

5.1.2.2 Image acquisition

Patients underwent CMR scans on a 1.5-T scanner (Magnetom Avanto, Siemens) with a standard 8-channel matrix coil configuration.

The imaging protocol consisted of three long-axis (four-, three-, and two-chamber view) and a full stack of short-axis steady-state free precession cine images as previously described. (41) T2weighted STIR(short tau inversion recovery) images were acquired on short-axis planes covering the entire left ventricle. This was followed by the acquisition of three short-axis slices (basal, mid-cavity, and apical) by using T1 and T2 mapping sequence (details of the sequences provided below).

Subsequently, acquisition of the same three short-axis slices (basal, mid-cavity, and apical) was repeated by using a segmented inversion-recovery gradient-echo sequence (IR-GRE) 1–3 minutes after the intravenous administration of 0.1 mmol/kg of gadobutrol (Gadovist; Bayer Schering Pharma, Berlin-Wedding, Germany) (early gadolinium enhancement EGE). Late gadolinium enhancement (LGE) images were acquired 15-20 minutes after contrast agent injection in the three long-axis and the full stack of short-axis views. (148)

5.1.2.3 T2w STIR

A breath-hold black-blood segmented turbo spin echo sequence was adopted for T2w STIR imaging, using a triple inversion recovery preparation module in order to suppress signal from flowing blood as well as from fat, with surface coil normalization. (182) Typical imaging parameters were TR 2 R-to-R intervals, TE 75 ms, flip angle 90°, TI 170 ms, slice thickness 8 mm, no interslice gap, field of view 340–400 mm, matrix 208 × 256, and a voxel size of 2.3 × 1.4 × 8 mm. Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate. To accommodate poor breath-holders, turbo factor was increased as necessary.

5.1.2.4 T2 Mapping Sequence

The T2 mapping sequence was performed using a T2 prepared steady-state free precession sequence that generated three T2-weighted images, each with its own T2 preparation time (0, 24, and 55 msec). (183) These images were acquired in the transient state of single-shot steady-state free precession immediately after the T2 preparation pulse. The signal intensity in each image represented a different echo time along the T2 decay curve. The sequence was performed during seven heartbeats with two R-R intervals to allow for T1 recovery. Typical parameters were as follows: 223.77/1.12; flip angle, 70°; section thickness, 8 mm; field of view, 340–400 mm; matrix, 156 × 192; and voxel size, 2.3 × 1.9 × 8 mm. (148)

5.1.2.5 T1 mapping sequence

Myocardial T1-mapping was performed using the modified Look-Locker inversion recovery (MOLLI) sequence 5(3)3 (Siemens Healthcare, Germany). The 5(3)3 MOLLI

protocol was used to ensure more-complete recovery of the inversion pulse at higher heart rates by acquiring a set of images for at least 5 heart beats after the first inversion pulse, followed by a 3-beat pause and then acquiring a set of images after the second inversion pulse for at least 3 beats. The acquisition parameters were: pixel bandwidth, 977 Hz/pixel; echo time=1.12 ms; flip angle=35 degrees; matrix=256×144; and 8 mm slice thickness. A nonlinear least-square curve fitting and motion correction were performed at different inversion times with the set of images acquired to generate a pixel-wise colored T1 map by the scanner.(184)

5.1.2.6 Late gadolinium enhancement imaging

Images were acquired at least 15 min following administration of 0.1 mmol/kg gadobutrol. LGE images were obtained using an inversion recovery prepared breath-hold gradient-echo technique. Typical image parameters were TR 700 ms, TE 4.33 ms; matrix 256 × 256; flip angle 30°; slice thickness 8.0 mm, no interslice gap, and voxel size 1.7 × 1.4 × 8 mm. The inversion time was progressively optimized to null normal myocardium (typical values, 250–350 ms). Images were acquired on both the long- and short-axis planes covering the entire left ventricle. Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate

5.1.2.7 Image analysis

Using Argus software (Siemens, Germany), regions of interest were drawn within T1 and T2 map in the remote myocardium (180° to infarct, with no regional wall motion abnormality, no oedema and no late gadolinium enhancement), salvaged myocardium, infarct core and microvascular obstruction(MVO) or intramyocardial

haemorrhage (if present) corresponding to the T2w STIR and LGE images, as previously reported. (148) **Figure 5-1**

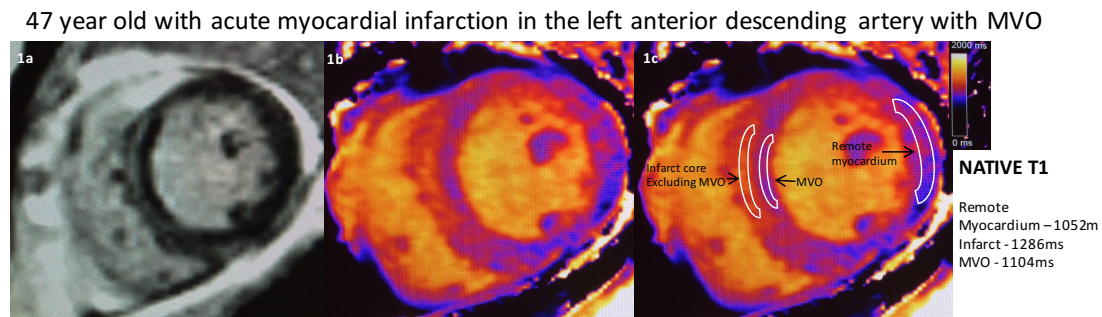


Figure 5-1 1a-c) 47 year old with acute myocardial infarction in the left anterior descending artery with MVO, a) LGE showing Septal hyperintensity (Infarct) with hypointense area (MVO), b) corresponding T1 map from the same slice position, c) Native T1 analysis – remote myocardium, infarct core and MVO.

Images were randomized for analysis. All measurements were performed by two observers (A.G.D. and E.M., SCMR/ESC CMR level 3) blinded to clinical and angiographic data, and previous image analysis. Hypointense areas in the T2w STIR and LGE images (representing IMH and MVO, respectively), when present, were included in the infarct size calculation whereas for infarct core analysis it was excluded. The infarct size was calculated from the LGE images by computer assisted planimetry and expressed in % of the total LV volume by using AHA 16-segment LV division and taking into account the number of quartiles involved in each segment.(185,186) In each patient 'global native T1' and 'global T2' was derived by taking the mean T1 and T2 of all 3 short axis slices. Image quality was subjectively visually graded 1 or 2 (1 = good and 2 = suboptimal/non diagnostic). Images were suboptimal/non diagnostic if there was artefact or signal loss that interfered with the

ability of the observers to interpret the image. No images were excluded because they were non diagnostic.

5.1.2.8 Statistical analysis

Statistical analysis was performed using SPSS V.23 (Armonk, New York, USA: IBM Corp.). Categorical variables were analysed using Fisher's exact test. Data are expressed as mean \pm SD where appropriate. Normally distributed continuous variables were compared using one-way analysis of variance with Bonferroni correction for multiple comparisons. Continuous variables that were not normally distributed were compared by Kruskal–Wallis tests. R-values quoted are for Pearson's correlation coefficient. Univariable and multivariable logistic regression analyses were performed to identify associates of MVO. Significance was defined as two-tailed $p < 0.05$, where p values presented include Bonferroni adjustment for multiple comparisons where appropriate.

5.1.3 Results:

5.1.3.1 Acute STEMI patients:

The demographics and CMR characteristics are shown in **Table 5-1**. Every patient had transmural and /or subendocardial LGE in the culprit artery territory with elevated troponin T level and at least 1 or more dysfunctional myocardial segment thereby confirming acute myocardial infarction. MVO was present in 53% ($n=16$) and IMH in 17% ($n=5$). None of the images were suboptimal.

Table 5-1 Demographic/CMR characteristics table

Characteristics	Control (n=20)	Acute MI (n=30)
Age, years	57(±13)	61(±10)
Female Sex, %	25%	20%
Smoking, %	-	27
Hypertension, %	-	43
Diabetes, %	-	10
CMR		
LV EF %	66(±7)	51(±9)
EDV ml	146(±35)	152(±29)
ESV ml	51(±18)	77(±26)
SV ml	95(±22)	75(±13)
Infarct size %	-	21(±10)

5.1.3.2 T1 and T2 mapping infarct characteristics

The native T1 and T2 values were analysed for each of the acute infarct characteristics ie remote myocardium, salvaged myocardium, infarct core, MVO and IMH. The peak native T1 was noted in the infarct core (1308 ± 71 ms) which was significantly higher than the other infarct characteristic categories on a pairwise comparison with Bonferroni correction ($p < 0.001$). The native T1 was slightly lower in the area of salvaged myocardium (1132 ± 53 ms) and microvascular obstruction (1128 ± 60 ms) with further reduced values in remote myocardium (1028 ± 34 ms) and area of intramyocardial haemorrhage (1034 ± 56 ms). **Figure 5-2**

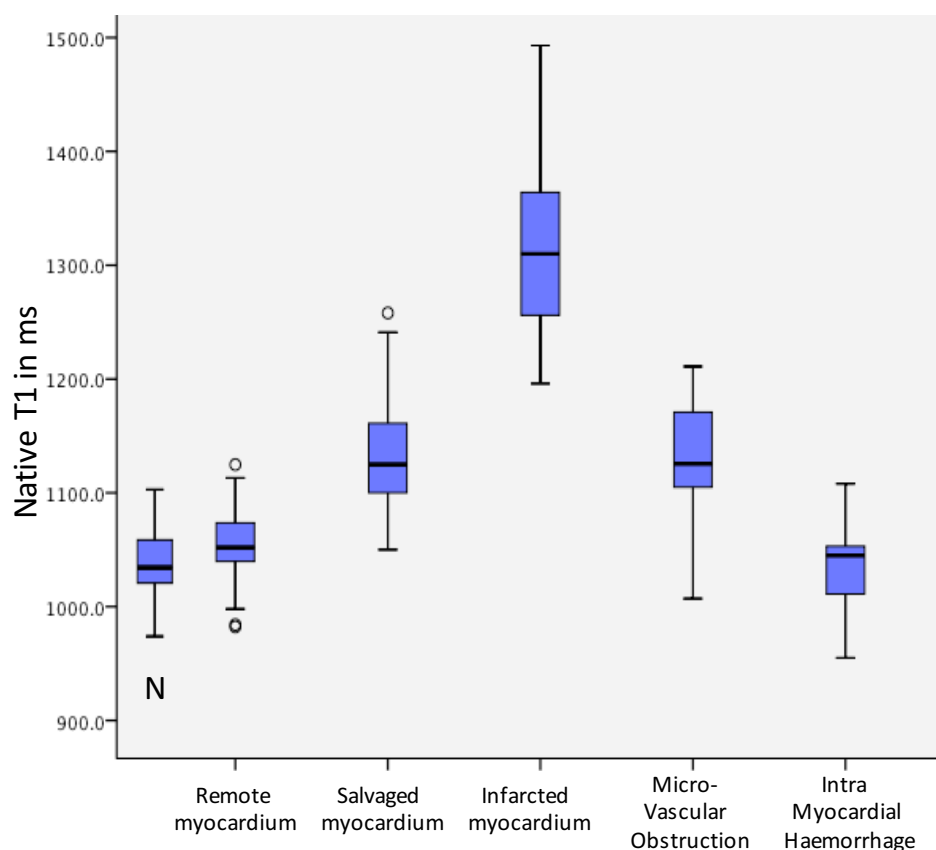


Figure 5-2 Boxplot: showing native T1 value in remote myocardium, salvaged myocardium, infarcted myocardium, microvascular obstruction and intramyocardial haemorrhage. N= Normal

A similar trend was also noted in the T2 mapping. The respective T2 values for the different infarct characteristics were – remote myocardium $54\pm 3\text{ms}$, Infarct core $71\pm 5\text{ms}$, salvaged myocardium $61\pm 3\text{ms}$, MVO $61\pm 3\text{ms}$ and IMH $53\pm 4\text{ms}$. **Figure 5-3**

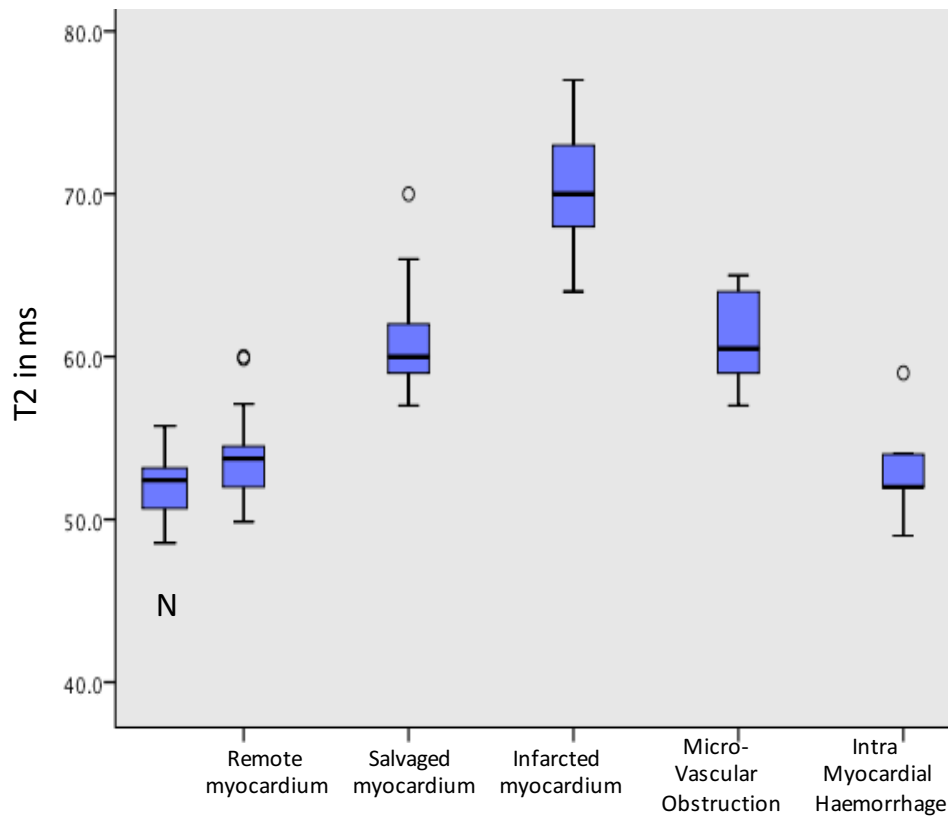


Figure 5-3 Boxplot: showing T2 value in remote myocardium, salvaged myocardium, infarcted myocardium, microvascular obstruction and intramyocardial haemorrhage. N= normal

5.1.3.3 Area at risk assessment by advanced relaxometry technique

The mean myocardial infarct size was $20.8\pm 10.2\%$ of the LV. There was no difference in either the mean AAR ($30.1\pm 11.7\%$ of the LV versus $34.3\pm 13\%$ of the LV, $P = 0.19$) or myocardial salvage index (0.14 ± 0.1 versus 0.11 ± 0.08 , $P = 0.18$) between the T1(threshold 2SD above the remote myocardium) and T2(threshold 2SD above the

remote myocardium) mapping techniques. On a per-patient analysis, there was an excellent correlation between T1 mapping and T2 mapping in the quantification of the AAR with an R of 0.91 ($P < 0.001$), with no bias (mean \pm 1.96SD: bias 0.04 \pm 10%) (Figure 5-4).

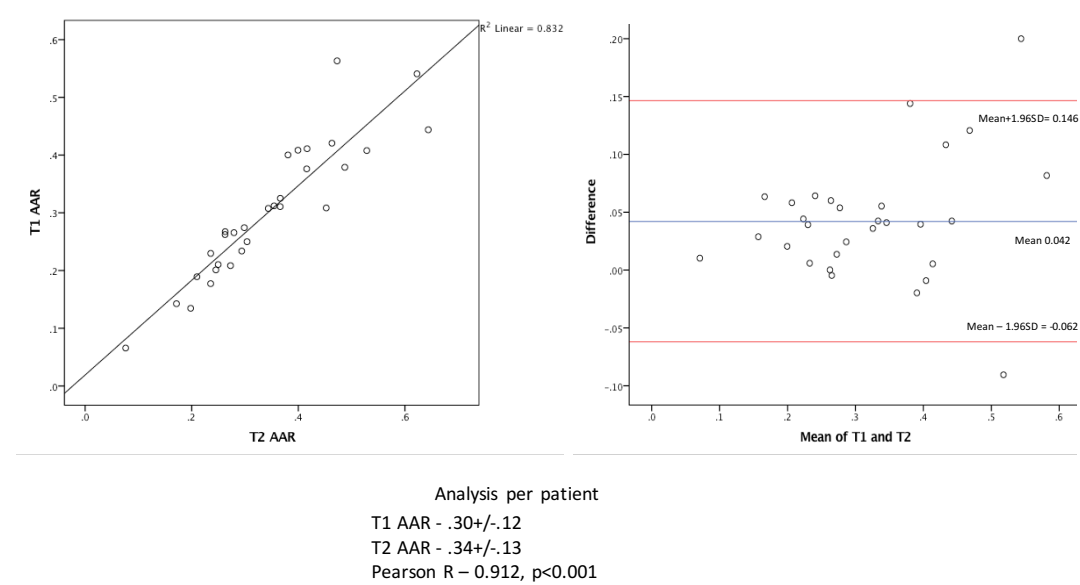


Figure 5-4 Bland-Altman plot comparing area at risk measured by native T1mapping with AAR measured by T2 mapping

5.1.3.4 MVO

Of 30 STEMI patients 16 had MVO. In these 16 patients, the T1Remote was higher when compared to remaining 14 without MVO (1048 \pm 20 vs 1004 \pm 32ms; $P < 0.001$).

There were no significant differences in T2Remote between those with and without MVO. **Table 5-2**

Table 5-2 CMR characteristics with and without MVO

CMR Characteristics	MVO (n=16)	No MVO (n=14)	P -value
LV EF %	49(±10)	53(±8)	0.28
EDV ml	161(±21)	141(±29)	0.05
ESV ml	84(±23)	69(±26)	0.15
SV ml	78(±15)	72(±10)	0.2
LV Mass gm	152(±20)	128(±29)	0.01
Infarct size %	22(±9)	14(±10)	0.04
AAR % (T2STIR)	34(±13)	27(±10)	0.12
T1 Remote ms	1048(±19)	1004(±33)	<0.001
T2 Remote ms	48(±2)	48 (±3)	0.8
T1 core ms	1128(±60)	1304(±67)	<0.001
T2 core ms	61(±3)	69(±4)	0.64

5.1.3.5 Associates of increased widespread injury

Impact of MVO and infarct size and other prognostic markers on remote myocardium were assessed using univariable and multivariable linear regression analysis. Native T1 values of remote myocardium were significantly higher in patients with MVO and in patients with a large MI size. A multivariate regression analyses showed presence of MVO to be independently associated with remote zone native T1. No association between infarct size and remote native T1 was found when corrected for presence of MVO. **Table 5-3**

Similarly, ECV values of remote myocardium were significantly higher in patients with MVO and in patients with a large MI size at baseline. A multivariate regression analyses showed presence of MVO to be independently associated with remote zone ECV. No association between infarct size and ECV was found when corrected for presence of MVO. **Table 5-3**

Table 5-3 Associates of increased widespread tissue injury - Univariable and multivariable logistic regression analysis

Variable	B (95% CI)	Stan. Beta	p- value	B (95% CI)	Stan. Beta	p- value
Native T1						
MVO	43.70 (23.79-63.62)	4.5	<0.001	30.68 (8.63-52.73)	2.87	0.008
Infarct Size	1.2 (0.19-2.22)	2.4	0.22	-		
Troponin	40.72 (14.24-67.2)	3.1	0.004			
indexedEDV	0.81 (-0.07-1.7)	1.87	0.07			
indexedLVmass	0.94 (-0.11-1.99)	1.83	0.08			
ECV						
MVO	0.03 (0.02-0.04)	5.32	<0.001	0.02 (0.01-0.04)	3.55	0.002
Infarct Size	0.001 (0.0002-0.002)	2.66	0.013			
Troponin	0.023 (0.002-0.044)	2.24	0.033			
Sex	0.0005 (-0.044-0.0002)	-2.02	0.05			
indexedLVmass	0.0009 (0.0002-0.001)	2.77	0.01			

ROC analysis demonstrated an excellent AUC of 0.92($p<0.001$) for remote native T1 in predicting MVO. **Fig 5-5**

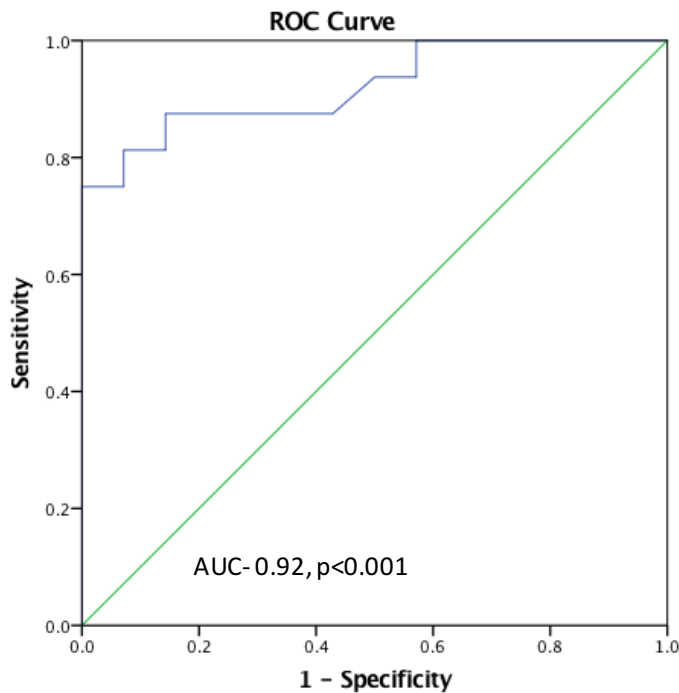


Figure 5-5 ROC showing the accuracy of remote native T1 in predicting the presence of MVO

5.1.3.6 Interobserver and intraobserver variability for segmental T1 measurement

There was excellent inter and intra-observer agreement for native segmental T1 measurement. The intraclass correlation coefficient (ICC) and 95% confidence interval were 0.968 (0.958-0.976) for interobserver and 0.992(0.967-0.998) for intraobserver agreement respectively.

5.1.4 Discussion

Our study looked at the non-invasive non contrast tissue characterisation in acute reperfused STEMI using advanced CMR relaxometry technique (native T1 and T2 mapping). The native T1 and T2 values had a distinctive profile for each of the

infarct characteristics with peak value in the infarct core and lowest values in areas of intramyocardial hemorrhage. We also looked at the impact of acute MI on the remote myocardium via non-invasive non-contrast imaging. We demonstrate that native T1 in remote myocardium are also elevated when compared to normal healthy myocardium (healthy volunteers). Previous autopsy studies demonstrated widespread myocardial inflammation as evidenced by activated T-cell lymphocyte infiltrate in both the remote and peri-infarct regions. (179,187) The findings in our study of elevated T1 and T2 in the remote myocardium may be secondary to those changes.

The findings of acute changes to remote myocardium are in keeping with previous literature by Carrick et al and Bulluck et al. (180,181)

The remote native T1 was significantly associated with microvascular injury and the association remained significant even correcting for infarct size, peak troponin and LV mass. However presence of MVO was not associated with the LVEF, LV size, pain to balloon time, infarct core native T1, infarct core T2, T2 remote or area at risk.

One of the limitations of native T1 mapping in acute MI is the difficulty in accurately quantifying infarct size without LGE. This is partly due to the reduction in T1 value in presence of MVO/IMH as well as the extent of salvaged myocardium which affects the T1 but not the infarct size. However, presence of MVO, which a poor prognostic marker, can be suggested by non-contrast remote native T1.

We also noted that the native T1 and T2 at the infarct core is reduced in presence of MVO or IMH. These may explain the findings noted by Carrick et al (188) that a lower T1 value within the infarct core was associated with poor prognosis, representing MVO/IMH.

We have used a robust and reproducible study design. The T1 and T2 mapping were done in the 3 short axis slices (base, mid, apical) in all the study subjects thereby covering the 16 AHA segments. The T1 and T2 analysis was done from the T1 and T2 maps which were available immediately on the scanner console with no need for post-processing. Apical slices were not excluded from analysis unlike other similar studies on T1 mapping due to the potential for partial volume averaging. (189) Similar studies have often eliminated lateral wall infarcts due to off-resonance artefact. (189) Our study sample had infarcts in all the different coronary territories including the lateral wall (which we included) to reduce the selection bias and reflect real world practice. Moreover, a recent study on T1 mapping in normal healthy volunteers has shown a regional variation with higher value in the septum compared to lateral wall. (190) The finding is particularly important in disease with regional affection like myocardial infarction.

5.1.4.1 Study Limitations

Our study sample size was small although the findings were highly statistically significant. We should have performed a follow up scan to compare the T1 and T2 mapping findings. However, following the same patient and comparing them with

the acute scan introduces the same patient bias. In order to overcome that problem we used presence of microvascular injury in the acute scan as the surrogate prognostic marker. Quality assessment of quantitative T1 and T2 maps was done by visual assessment. The verification of T1/T2 curve fit to ensure that the parametric quantitative maps were of good quality with good curve fit was not done. There is a small chance that a mistriggered acquisition could have produced underestimated T1 or T2.

5.1.5 Conclusions

The study looked at the infarct characteristics via non-invasive tissue characterisation by advanced CMR relaxometry technique. Our study highlights that in STEMI the remote myocardium is also affected when compared to normal healthy myocardium which is consistent with previously published studies. The native T1 in remote myocardium is independently associated with microvascular injury.

5.2 *Non contrast assessment of viability with T1 mapping*

5.2.1 Introduction

Acute myocardial infarction leads to reversible (viable/stunned) and irreversible(non-viable) myocardial injury, even after successful coronary reperfusion. Early recognition of viable myocardium after a myocardial infarction(MI) is of clinical relevance as the affected segments have the potential for recovery. Targeted revascularization of viable myocardium improves clinical outcomes. Hence viability assessment is a key aspect in the management of ischaemic heart disease (IHD). Late gadolinium enhancement (LGE) CMR is increasingly used in clinical practice as a viability assessment tool (132,191). LGE viability assessment is performed by analyzing the extent of scar thickness, with a myocardial segment $\geq 75\%$ transmural extent deemed mostly non viable. The transmural extent of infarct (TEI) assessed by LGE has been shown to be inversely related to functional recovery after reperfusion (42,118). LGE imaging requires administration of gadolinium-based contrast agents. The use of these contrast agents is limited in patients with moderate to severe renal dysfunction due to the potential risk of nephrogenic systemic fibrosis.(192) In addition there have been several reports of gadolinium-based deposits in the central nervous system structures following repeated use of gadolinium contrast, whose clinical meaning is still uncertain. (193) An alternative viability imaging method that might obviate the use of contrast-agents is desirable. Myocardial T1 mapping is emerging as a novel non-contrast CMR imaging tool in the assessment of non-IHD and IHD (194). Native T1 mapping technique is highly

sensitive to changes in myocardial tissue, thereby providing excellent tissue characterization obviating for the need for contrast administration. Kali et al. looked at diagnostic accuracy of T1-mapping in the detection of overall transmural in chronic MI using a thresholding-based detection.(195) We tested the hypothesis that native segmental T1 mapping can assess the TEI thereby differentiating between viable and non-viable myocardium in IHD without the use of gadolinium contrast.

5.2.2 Aim:

The aim of the study was to compare the performance of native segmental T1 mapping in quantifying the TEI/myocardial scarring with LGE in chronic as well as acute MI patients using a 1.5T CMR.

5.2.3 Methods:

5.2.3.1 Study population

60 patients with myocardial infarction were recruited: 30 successfully re-perfused STEMI patients (mean age 61 ± 10 years and 80% males) scanned at day 2 and 30 chronic MI patients (>1 year after MI) (mean age 67 ± 10 years and 80% males). All patients were diagnosed with MI according to guidelines. (6,138) Exclusion criteria were: general contraindications to CMR, chronic atrial fibrillation, renal impairment with $eGFR < 30$, and cardiogenic shock. 20 age- and sex-matched healthy volunteers served as control (all free of cardiovascular disease). The study was approved by the local Institutional Research and Innovation department. All patients gave informed

written consent. Findings were compared with 20 healthy volunteers with no previous medical history (mean age 59 ± 16 yrs, 75% male).

5.2.3.2 Image acquisition

Patients underwent CMR scans on a 1.5-T scanner (Magnetom Avanto, Siemens) with a standard 8-channel matrix coil configuration.

The imaging protocol consisted of three long-axis (four-, three-, and two-chamber view) and a full stack of short-axis steady-state free precession cine images as previously described. (41) This was followed by the acquisition of three short-axis slices (basal, mid-cavity, and apical) by using T1mapping sequence (details of the sequence provided below). Subsequently, acquisition of the same three short-axis slices (basal, mid-cavity, and apical) was repeated by using a segmented inversion-recovery gradient-echo sequence (IR-GRE) 1–3 minutes after the intravenous administration of 0.1 mmol/kg of gadobutrol (Gadovist; Bayer Schering Pharma, Berlin-Wedding, Germany) (early gadolinium enhancement EGE). Late gadolinium enhancement (LGE) images were acquired 15-20 minutes after contrast agent injection in the three long-axis and the full stack of short-axis views. (148) In acute MI cohort T2weighted STIR(short tau inversion recovery) images were acquired on short-axis planes covering the entire left ventricle prior to gadolinium administration.

5.2.3.3 Late gadolinium enhancement imaging

Images were acquired at least 15 min following administration of 0.1 mmol/kg gadobutrol. LGE images were obtained using an inversion recovery prepared breath-hold gradient-echo technique. Typical image parameters were TR 700 ms, TE 4.33 ms; matrix 256×256 ; flip angle 30° ; slice thickness 8.0 mm, no interslice gap, and voxel size $1.7 \times 1.4 \times 8$ mm. The inversion time was progressively optimized to null normal myocardium (typical values, 250–350 ms). Images were acquired on both the long- and short-axis planes covering the entire left ventricle. Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate

5.2.3.4 T1 mapping sequence

Myocardial T1-mapping was performed using the modified Look-Locker inversion recovery (MOLLI) sequence 5(3)3 (Siemens Healthcare, Germany). The 5(3)3 MOLLI protocol was used to ensure more-complete recovery of the inversion pulse at higher heart rates by acquiring a set of images for at least 5 heart beats after the first inversion pulse, followed by a 3-beat pause and then acquiring a set of images after the second inversion pulse for at least 3 beats. The acquisition parameters were: pixel bandwidth, 977 Hz/pixel; echo time=1.12 ms; flip angle=35 degrees; matrix= 256×144 ; and 8 mm slice thickness. A nonlinear least-square curve fitting and motion correction were performed at different inversion times with the set of images acquired to generate a pixel-wise colored T1 map by the scanner.(196)

5.2.3.5 T2w STIR

A breath-hold black-blood segmented turbo spin echo sequence was adopted for T2w STIR imaging, using a triple inversion recovery preparation module in order to suppress signal from flowing blood as well as from fat, with surface coil normalization. (182) Typical imaging parameters were TR 2 R-to-R intervals, TE 75 ms, flip angle 90°, TI 170 ms, slice thickness 8 mm, no interslice gap, field of view 340–400 mm, matrix 208 × 256, and a voxel size of 2.3 × 1.4 × 8 mm. Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate. To accommodate poor breath-holders, turbo factor was increased as necessary.

5.2.3.6 Image analysis

Argus software (Siemens, Germany) was used for the quantification of LV volumes and ejection fraction (EF) (197). Segmental TEI was assessed by contouring the area of LGE and dividing it by the area of the whole segment using full width at half maximum (FWHM) technique using CVI42 software (Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

A scar transmural scale of 0-4 was used for the 16 AHA segment (0=no scar, 1= 1-24%, 2=25-49%, 3=50-74% and 4=≥75% scar thickness). A scar transmural grade of 3 or less (<75% TEI) was deemed viable. (118,198) Observer blinded to the LGE data (AGD) drew regions of interest within the native T1 map in each of the American Heart Association (AHA) 16 segments in the short axis motion corrected maps using Argus software, adjusting for partial-voluming and/or artefact, as previously described. (199) **Figure 5-6** The LGE data was blinded for the T1 mapping analysis in

order to test the hypothesis that T1 mapping can assess viability without the need of LGE. Images were randomized for analysis. In patients with acute MI, the hypointense areas in the LGE images (representing MVO), when present, were included in the contoured areas for the segment wise calculation of TEI. The infarct size was calculated from the LGE images by semi-automated software based analysis (FWHM) and expressed in % of the total LV volume. Another observer drew ROIs (GP) in the infarct core and remote myocardium in the T1 maps corresponding to the LGE image(unblinded). Remote myocardium was defined as myocardial tissue 180degree to the infarct with no evidence of hyperenhancement or myocardial oedema, as previously described.(180) Analysis was also done as per the coronary artery territory. Myocardial segments were assigned to coronary arteries as described in the AHA 16 segment model(excluding the apical cap), with 6 segments for the left anterior descending artery, 5 for the right coronary artery, and 5 for the left circumflex artery. (200) In each patient 'global native T1' was derived by taking the mean T1 of all 16 AHA segments. Images were suboptimal/non diagnostic if there was artefact or signal loss that interfered with the ability of the observers to interpret the image. This was observed in 3 patients but to overcome the problem the sequences were repeated. In the final analysis no images were considered non-diagnostic.

54 year old with acute transmural myocardial infarction in right coronary artery

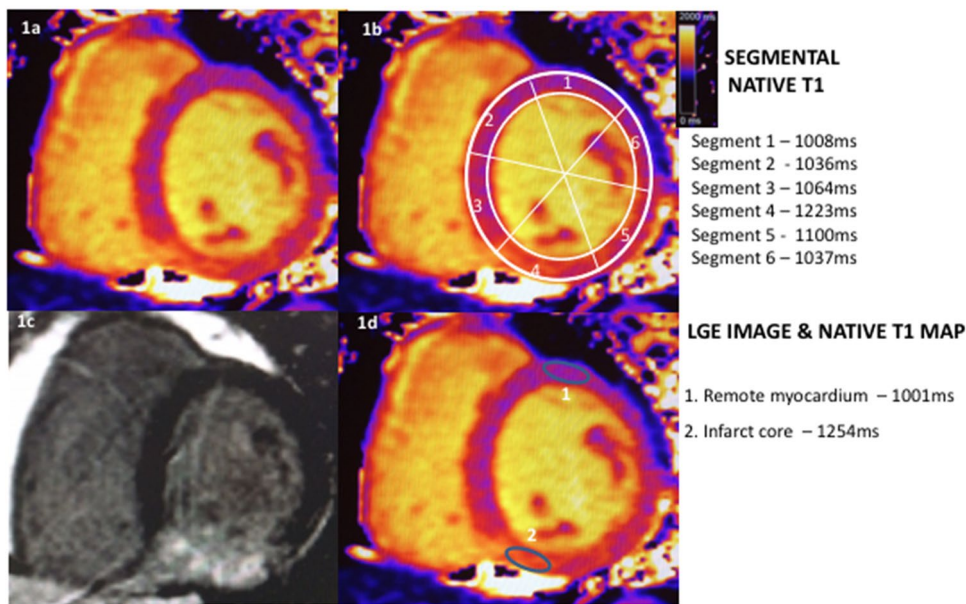


Figure 5-6 CMR images from a 54 year old with acute transmural myocardial infarction in right coronary artery, 1a) T1 map of the short axis, 1b) Region of interest drawn in each of the segment with corresponding native T1 value (blinded to LGE image), 1c) LGE image in the short axis, 1d) T1 map of the corresponding short axis with region of interest in the remote myocardium and infarct core(unblinded to LGE image)

5.2.3.7 Statistical analysis

Statistical analysis was performed using SPSS V.23 (Armonk, New York, USA: IBM Corp.) and R version 3.1.2 (R Core Team 2014). Categorical variables were analyzed using Fisher exact tests. Normally distributed continuous variables were expressed as mean±standard deviation and compared using unpaired Student t tests or one-way analysis of variance with Bonferroni post hoc correction for between-groups comparisons, as appropriate. Continuous variables that were not normally distributed were compared by Kruskal–Wallis tests. R-values quoted are for Pearson's correlation coefficient. The potential of quantitative T1-mapping to assess

the TEI or viability on a segmental basis against the current gold standards of LGE were explored. The analysis was also performed as per each coronary artery territory. Interobserver (AGD and IH) and intraobserver (AGD) variability for segmental native T1 was assessed in 20 patients (10 acute MI and 10 chronic MI patients), and expressed as intraclass correlation coefficient (ICC) and 95% confidence interval.

Segmental analysis run a risk of class effect due to the potential of multiple samples from the same patient. To nullify the class-effect a series of generalized linear mixed effect models, with the random intercept for each person and for each segment, were performed to assess the association between T1 mapping and viability/LGE TEI. The models were used to account for the fact that different segments from the same patient or same segment location from different patients may not behave independently. These models were conducted for both acute and chronic MI assessments. Receiver operating characteristic (ROC) analysis was performed to identify area under curve (diagnostic accuracy) of native T1 as a marker of TEI by using corresponding LGE scoring (LGE score >3) as the gold standard. Cut-off values of T1 relaxation times as a marker of viability were also calculated from the ROC curve. Statistical significance of the differences between ROC curves was assessed using the online calculator (www.vassarstats.net). To take into consideration potential within-subject interaction of segments, clustered ROC analysis was also conducted to assess the performance of native T1 to predict viability. Significance was defined as two-tailed $p < 0.05$.

5.2.4 Results:

The demographic and the CMR characteristics of the healthy control and the patient cohort (60 MI patients- acute and chronic MI subgroups) are presented in **Table 5-4**.

The mean age of the healthy volunteers was 57 ± 13 yrs and 75% were male. The mean age was significantly lower in the acute MI group (61 ± 10 yrs vs 67 ± 10 yrs, $p=0.017$) compared to the chronic MI group. In 5% ($n=3$) of patients the T1 maps had artefacts or signal. To overcome this problem, the mapping images were repeated. Out of the 960 segments analysed from patients with previous MI (acute and chronic), 286 segments had evidence of LGE. Sixteen of the 30 acute MI patients had microvascular obstruction (MVO) (53%).

Table 5-4 Study population demographic and CMR characteristics

Characteristics	Control (n = 20)	Acute MI (n = 30)	Chronic MI (n = 30)	p-value (acute versus chronic)
Age (years)	57(± 13)	61(± 10)	67(± 10)	0.017
Female sex (%)	25%	20%	20%	1.0
Smoking (%)	–	27	17	0.356
Hypertension (%)	–	43	53	0.447
Diabetes (%)	–	10	23	0.171
CMR				
LV EF (%)	66(± 7)	51(± 9)	51(± 13)	0.833
EDV (ml)	146(± 35)	152(± 29)	167(± 56)	0.218
ESV (ml)	51(± 18)	77(± 26)	85(± 48)	0.406
SV (ml)	95(± 22)	75(± 13)	83(± 23)	0.144
Infarct size (%)	–	21(± 10)	16(± 12)	0.135

5.2.4.1 Interobserver and intraobserver variability for segmental T1 measurement

There was excellent inter and intra-observer agreement for native segmental T1 measurement. The intraclass correlation coefficient (ICC) and 95% confidence

interval were 0.968 (0.958-0.976) for interobserver and 0.992(0.967-0.998) for intraobserver agreement respectively.

5.2.4.2 Results - Chronic MI

T1 mapping vs scar transmurality (TEI)-In patients with chronic MI, the segmental T1 correlated significantly with LGE TEI ($R= 0.74$, $p<0.001$). **Figure 5-7.**

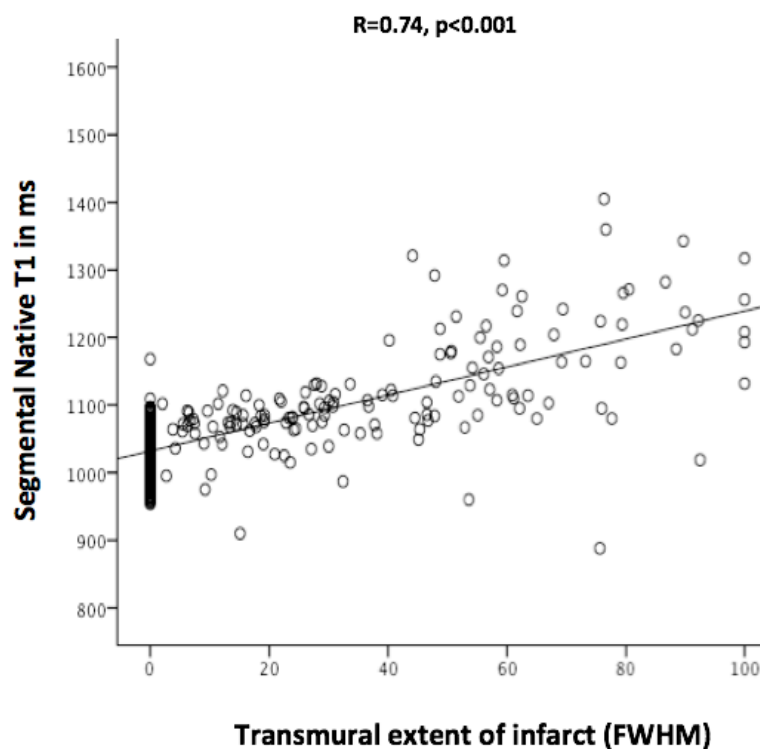


Figure 5-7 Scatter plot: chronic MI cohort showing native T1 value vs the TEI

The mean segmental T1 value for LGE negative segments (myocardial segments with no infarction) was $1,031\pm31$ ms, LGE positive but viable (scar grade 1-3): $1,103\pm57$ ms and LGE positive but non viable (scar grade 4): 1206 ± 118 ms. The mean segmental T1 in each of the 3 categories (no LGE, LGE positive but viable and LGE positive but non-

viable) were significantly different on a pairwise comparison with Bonferroni correction ($p<0.01$). **Figure 5-8** The mean native T1 in the infarct core and remote myocardium were $1171\pm 76\text{ms}$ and $1005\pm 19\text{ms}$ respectively. Table 5-5

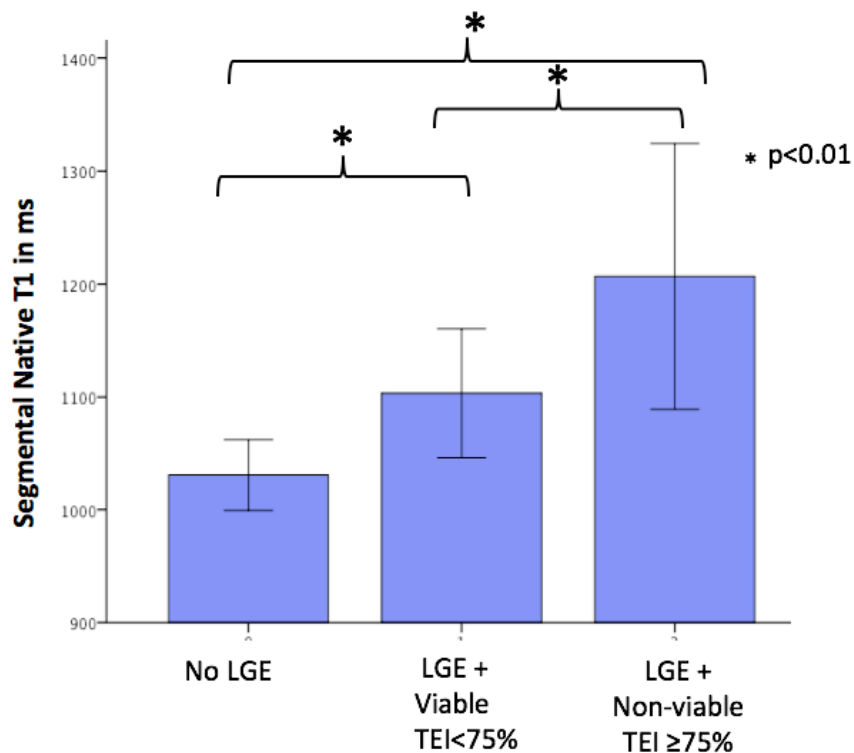


Figure 5-8 Bar diagram with error bar(SD): Chronic MI cohort showing segmental native T1 value in LGE negative, LGE positive with viability and LGE segments with non-viability

Table 5-5 Mean Native T1(in ms) in the LGE negative segments, LGE positive but viable segments, LGE positive non-viable segments, Infarct core and Remote myocardium

Category	LGE negative segments	LGE positive viable segments	LGE positive non-viable segments	Infarct core	Remote myocardium
Chronic MI Mean T1 (ms)±SD	1031±31	1103±57	1206±118	1171±76	1005±19
Acute MI Mean T1(ms)±SD	1054±65	1135±73	1168±71	1308±71	1054±65

When grouping the segments into coronary artery territories, the correlation between native T1 and LGE TEI for RCA, LCx and LAD territories were $R=0.77$, 0.80 , 0.69 respectively ($p<0.001$). **Figure 5-9**

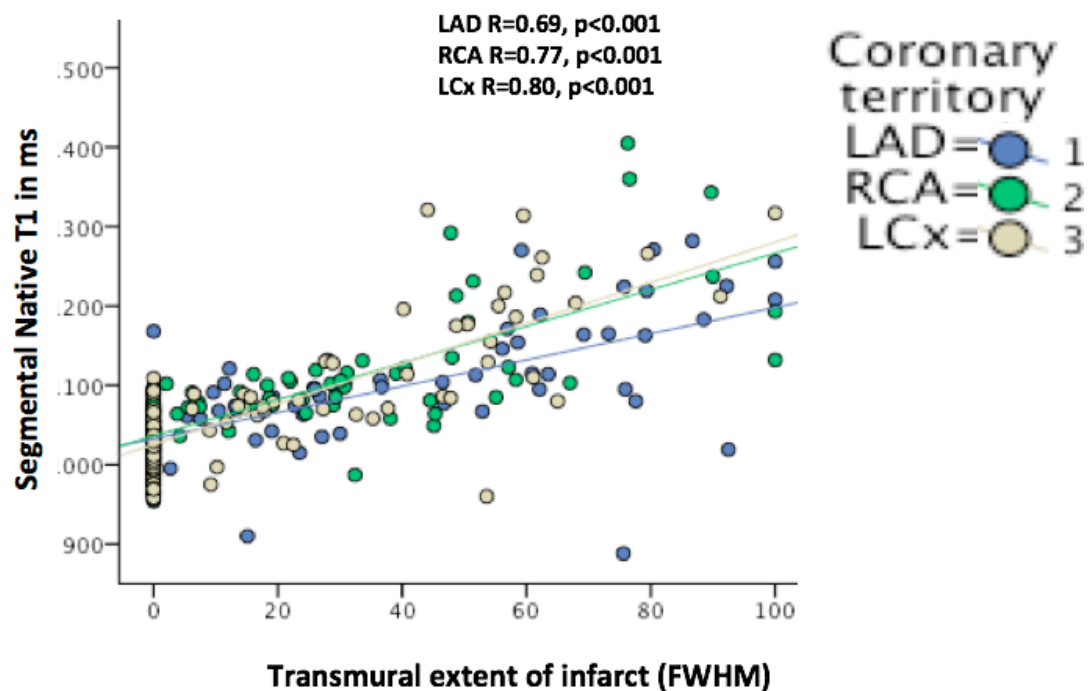


Figure 5-9 Scatter plot: Correlation between segmental T1 and Transmural extent of Infarct – as per coronary artery territory in chronic MI

T1 mapping as a marker of transmural extent of infarction -Native T1 mapping showed excellent diagnostic accuracy in predicting transmural LGE $\geq 75\%$ - AUC- 0.88 (CI 0.77 - 0.99 , $p<0.001$). **Figure 5-10** A cut-off of native T1 of $1,085$ ms differentiated viable from non-viable segments with 88% sensitivity and 88% specificity. Clustered ROC curve analysis showed that segmental T1 mapping had an AUC of 0.8338 (95% CI 0.7002 - 1.00) to predict viability.

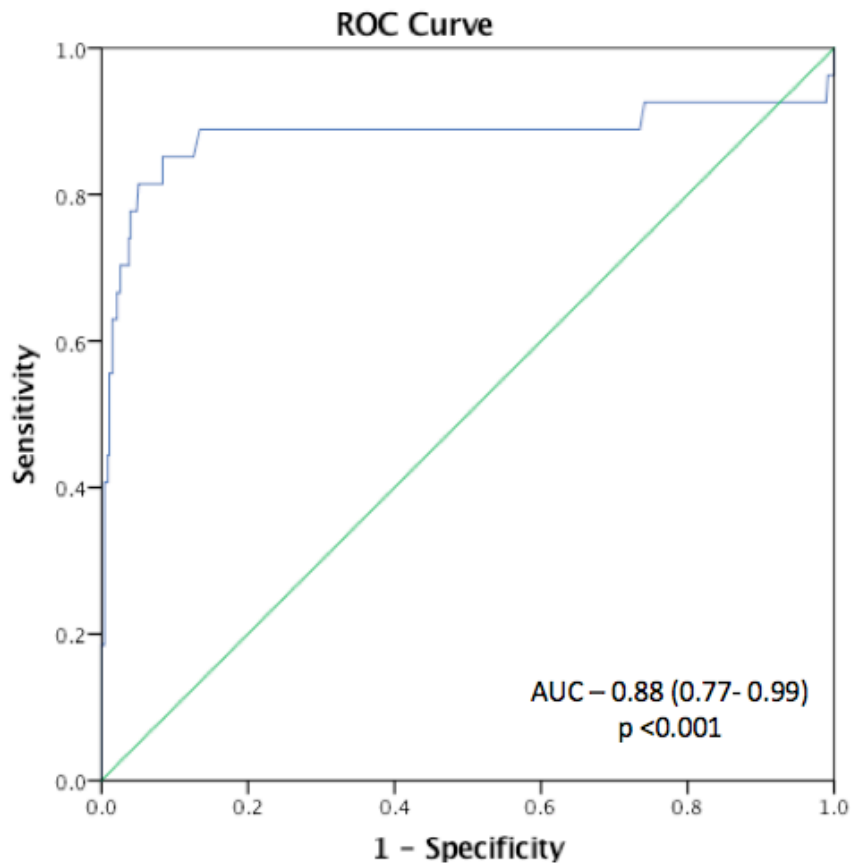


Figure 5-10 ROC curve: Chronic MI cohort comparing segmental native T1 vs LGE viability

Mixed effects model with random intercept - Generalized linear mixed effect models, with the random intercept to assess the association between native T1 and viability/TEI correcting for the class effect due to multiple segments from same person or same segment location. Presence of non viability was significantly associated with native T1 (Chi square 307.02, $p < 0.01$), increasing it by $131.9 \pm 6.3\text{ms}$ (standard errors). TEI significantly affected T1 (Chi square 388.9, $p < 0.01$), increasing it by $2.07 \pm 0.1\text{ms}$ (standard errors) for every percent increase in TE.

5.2.4.3 Results - Acute MI

T1 mapping vs scar transmuralty (TEI)- In patients with acute MI, the segmental T1 correlated significantly with LGE TEI with $R=0.57$, $p<0.001$. **Figure 5-11**

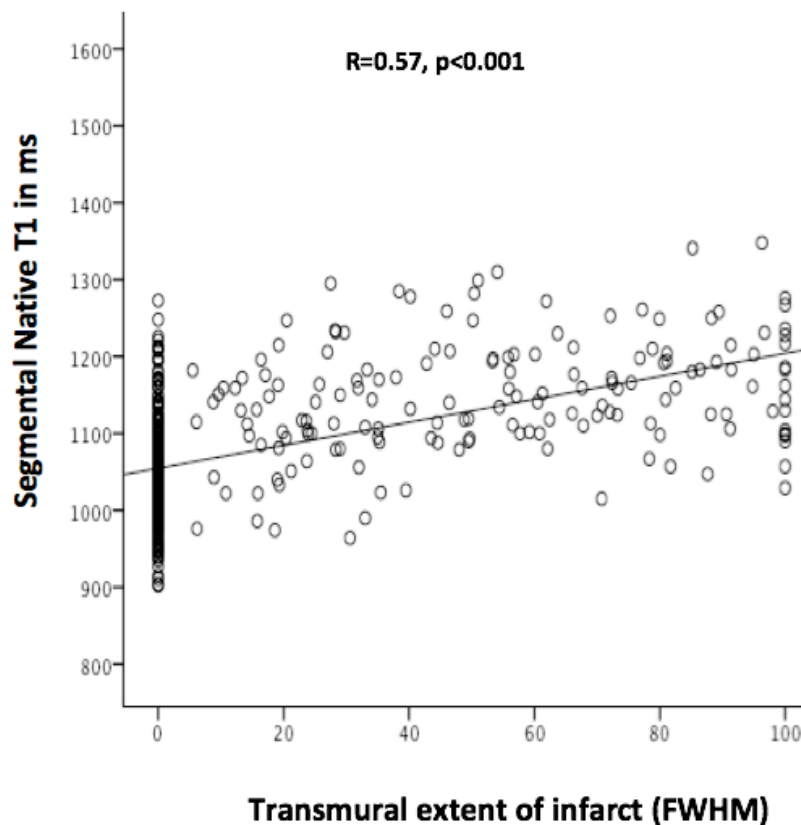


Figure 5-11 Scatter plot: Acute MI cohort showing native T1 value vs the LGE TEI,

The mean segmental T1 value for scar transmuralty grade 0 (no LGE) was $1,054\pm65\text{ms}$, LGE positive but viable (scar grade 1-3): $1,135\pm73\text{ms}$ and LGE positive but non viable (scar grade 4): $1,168\pm71\text{ms}$. The mean segmental T1 in the 3 categories (no LGE, LGE positive but viable and LGE positive but non-viable) were significantly different on a pairwise comparison with Bonferroni correction ($p<0.01$).

Figure 5-12 The mean native T1 in the infarct core was $1308\pm71\text{ms}$ **Table 5-5.**

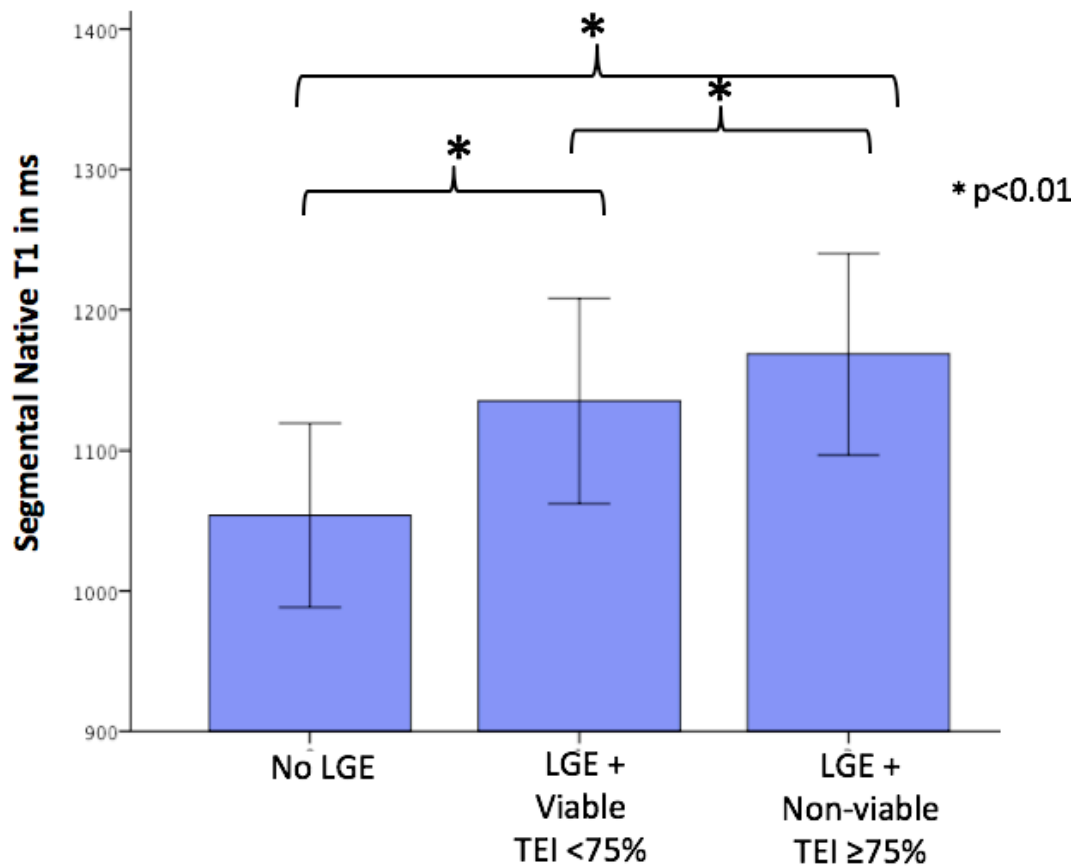


Figure 5-12 Bar diagram with error bar(SD): Acute MI cohort showing segmental native T1 value in LGE negative, LGE positive with viability and LGE segments with non-viability

When grouping the segments into coronary artery territories, the correlation between native T1 and LGE TEI for RCA, LCx and LAD territories were R=0.66, 0.57, 0.57 respectively(p<0.001). **Figure 5-13**

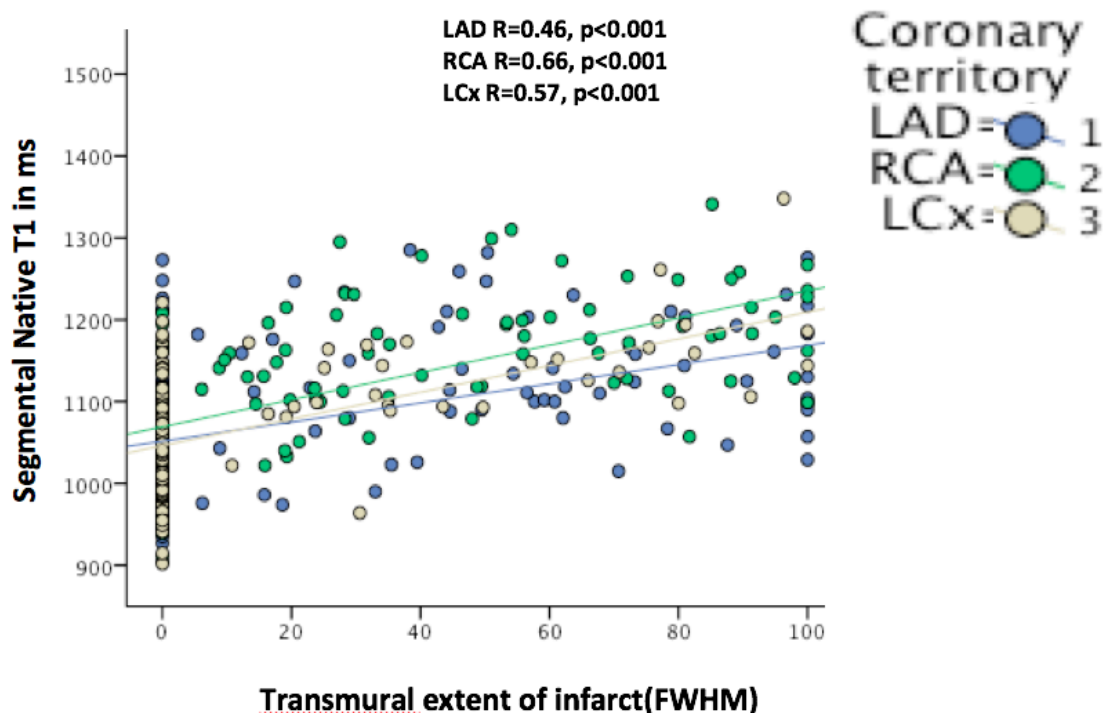


Figure 5-13 Scatter plot: Correlation between segmental T1 and Transmural extent of Infarct – as per coronary artery territory in acute MI

T1 mapping as a marker of transmural extent of infarction - ROC analysis of segmental native T1 in acute MI against gold standard LGE viability(>75%TEI) showed good diagnostic accuracy AUC-0.83(CI 0.78- 0.88, p<0.001). **Figure 5-14.** A T1 threshold of 1110ms most optimally differentiated viable from non-viable segments with 79% sensitivity and 79% specificity. Clustered ROC curve analysis showed that segmental T1 mapping had an AUC of 0.8338 (95% CI 0.7587-0.9088) to predict viability.

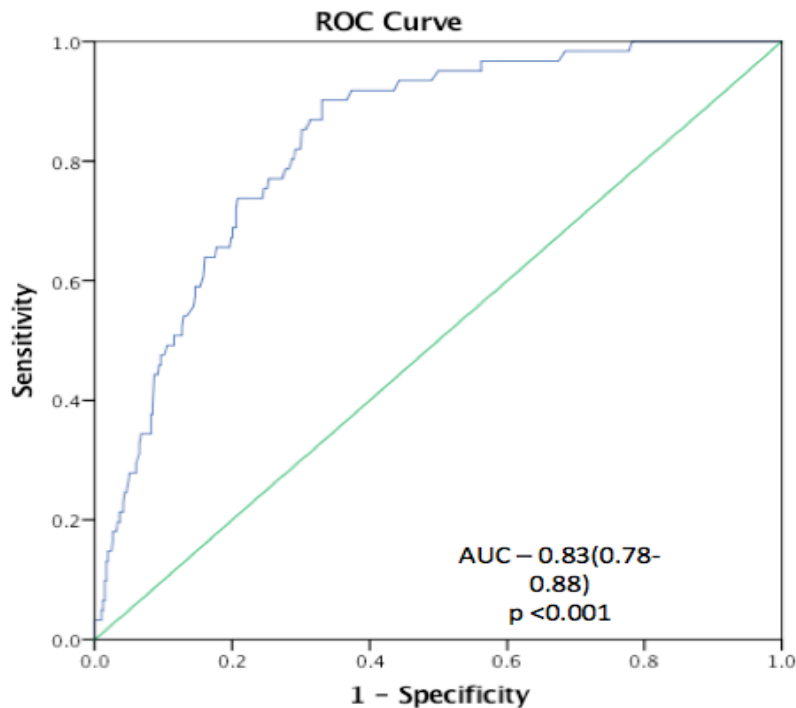


Figure 5-14 ROC curve: Acute MI cohort comparing segmental native T1 vs LGE viability

Mixed effects model with random intercept - Presence of non viability was significantly associated with native T1 (Chi square 145.4, $p < 0.01$), increasing it by 100.1 ± 7.7 ms (standard errors). TEI significantly affected native T1 (Chi square 206.1, $p < 0.01$), increasing it by 1.5 ± 0.1 ms (standard errors) for every percent increase in TEI.

T2w STIR area at risk (oedematous area) in acute MI- All the acute MI scans showed evidence of myocardial oedema in the infarct related artery territory. The area at risk (total area of oedema) in the acute MI was $31 \pm 12\%$ of the total LV.

5.2.4.4 Global native T1

Global native T1 in normal vs affected - Global native T1 in normal healthy volunteers was compared with all patients with previous MI (acute and chronic). The

mean global T1 in normal volunteers was 1028 ± 28 ms, which was significantly lower than patients with previous MI 1070 ± 36 ms, $p < 0.0001$. The global native T1 in patients with acute MI was 1082 ± 34 ms ($p < 0.0001$ vs normal volunteer), whereas for chronic MI it was 1058 ± 34 ms ($p = 0.002$ vs normal volunteer). **Figure 5-15**

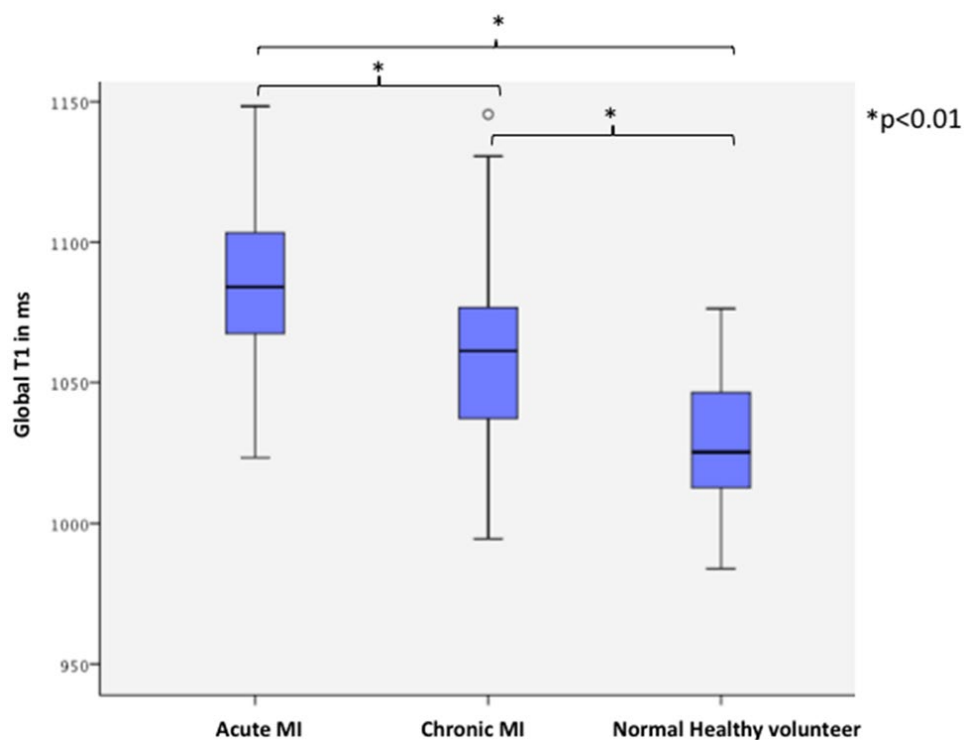
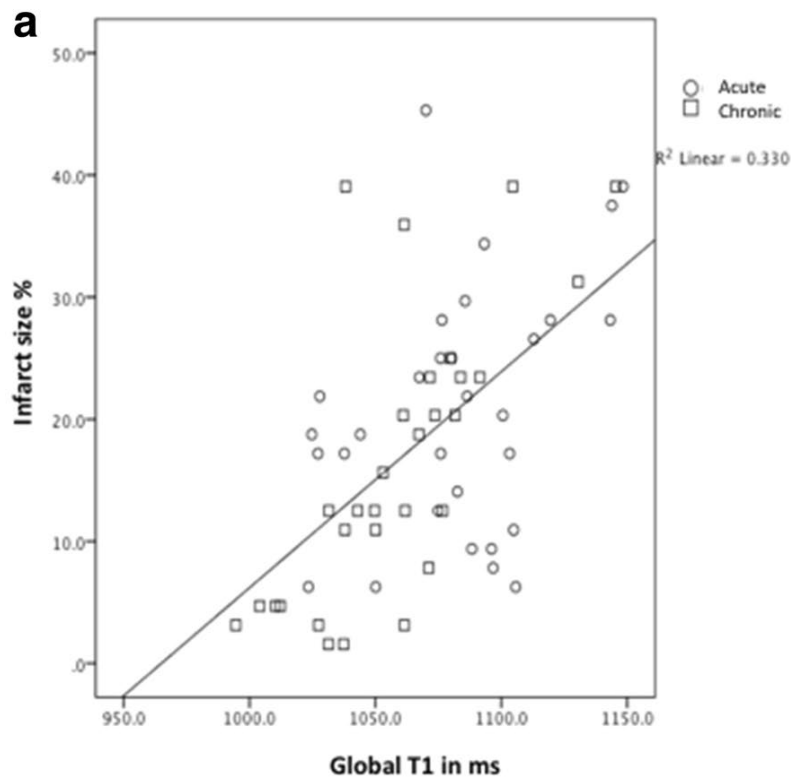


Figure 5-15 Boxplot showing the global native T1 in acute MI cohort, chronic MI cohort and the normal healthy volunteer

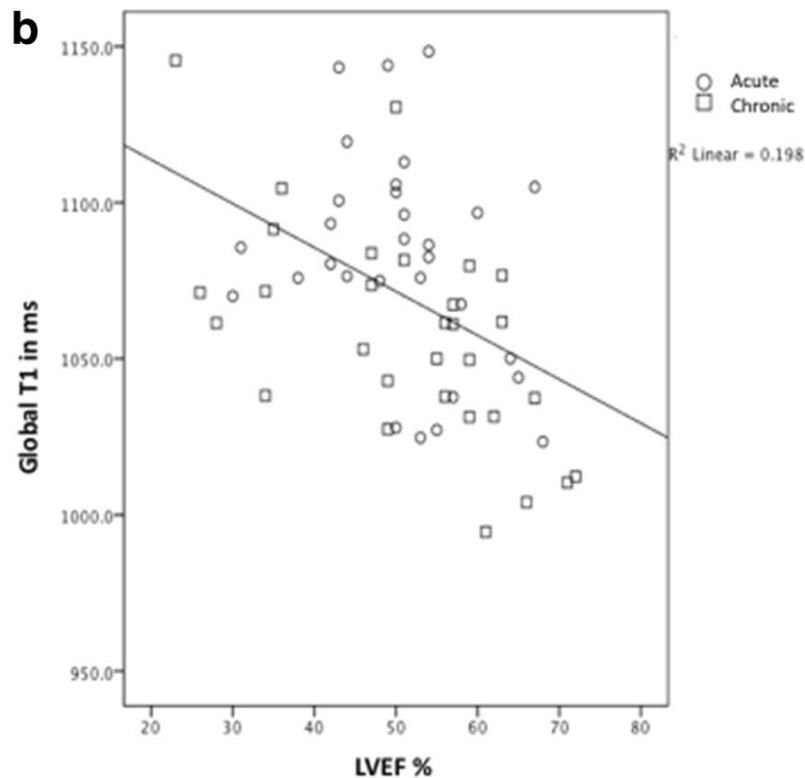
Global native T1 vs Infarct size - Global native T1 was compared with the infarct size. For the total cohort ($n=60$) it showed a good positive correlation $r = 0.575$, $p < 0.001$. Subgroup analysis: the correlation was found to be excellent in chronic MI $r=0.717$, $p < 0.001$ whereas for acute MI it was weakly significant $r=0.365$, $p=0.048$ **Figure 5-16**



	R value	P-value
Total cohort (n=60)	0.575	<0.001
Acute STEMI (n=30)	0.365	0.048
Chronic MI (n=30)	0.717	<0.001

Figure 5-16 Scatter plot showing the correlation between global T1 and infarct size

Global native T1 vs LV EF -Global native T1 was compared with the left ventricular ejection fraction. For the total cohort (n=60) it showed a significant inverse correlation $r = -0.445$, $p < 0.001$. Subgroup analysis: the correlation was found to be statistically significant in chronic MI $r = -0.596$, $p < 0.001$ but not in acute MI $r = -0.291$, $p = 0.118$. **Figure 5-17**



	R value	P-value
Total cohort (n=60)	-0.445	<0.001
Acute STEMI (n=30)	-0.291	0.118
Chronic MI (n=30)	-0.596	<0.001

Figure 5-17 Scatter plot showing the correlation between global T1 and LV ejection fraction

5.2.4.5 T1 mapping vs wall motion score vs wall thickness for the assessment of viability

Segmental native T1 was compared with segmental wall thickness and segmental wall motion score against gold standard LGE viability. ROC analysis of the 960 segments for viability assessment showed the highest diagnostic accuracy of T1 mapping (AUC - 0.9, 95%CI 0.87- 0.93, $p < 0.0001$) when compared to wall motion

score (AUC 0.837, $p < 0.0001$, 95%CI 0.8-0.875), and segmental wall thickness (AUC 0.453, $p = 0.07$, 95%CI 0.401-0.505). **Figure 5-18**

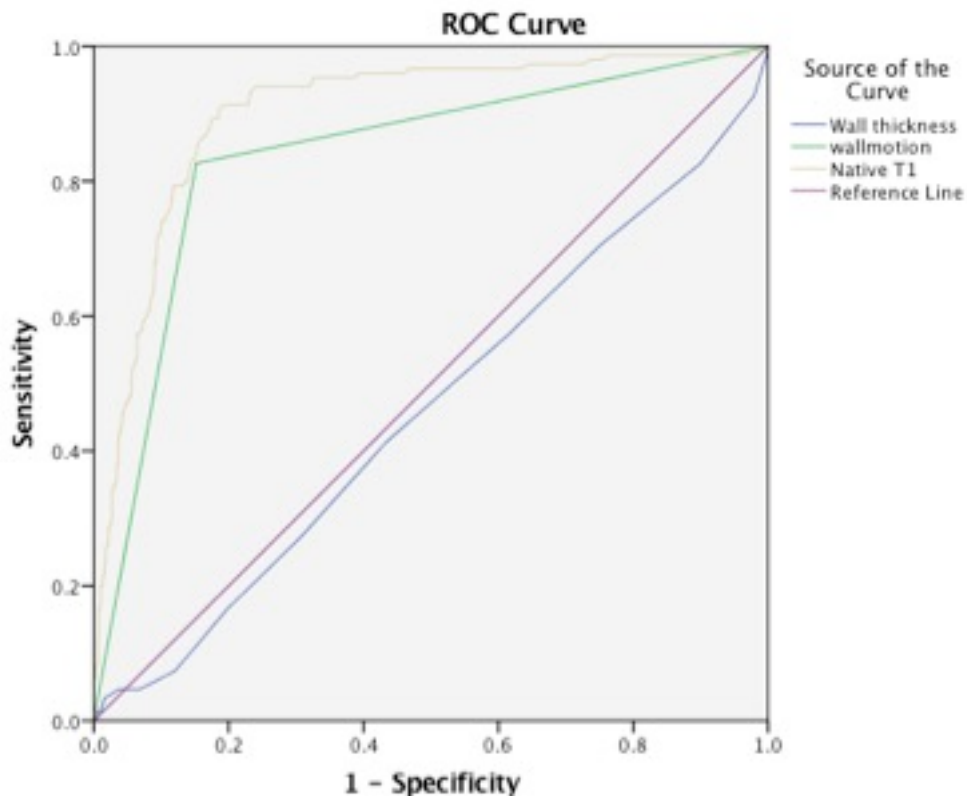


Figure 5-18 ROC curve: Segmental T1, segmental wall thickness, segmental wall motion vs gold standard LGE viability

5.2.5 Discussion

The study looked at the diagnostic performance of segmental T1 mapping as a marker of LGE TEI and myocardial viability in patients with previous MI (acute and chronic). Overall native segmental T1 mapping had an excellent diagnostic accuracy, in distinguishing viable from non-viable myocardium when using LGE $\geq 75\%$ transmural as a reference standard to define infarcted non-viable myocardium. Diagnostic accuracy was better when used in chronic MI (AUC -0.88) rather than acute MI (AUC -0.83). The clinical value of T1 mapping lies in the evaluation of

myocardial scar extent, on a voxel-wise basis, without the need to use a contrast agent.

Myocardial infarction is a regional disease affecting parts of the myocardium supplied by the occluded/stenosed coronary artery. Segmental analysis as per the AHA nomenclature is the most widely used cardiac imaging technique in current clinical practice. The study was designed to look at the T1 profile in different LGE TEI. In a segment wise analysis for T1 there was a statistically significant positive correlation between LGE TEI and the native T1 values. The association of native T1 and viability/TEI remained significant even adjusting for segments from same patient bias as well as same segment locations from different patient bias using the mixed effect model with random intercepts.

The opportunity to correlate presence and potential extent of infarction/scarring without the use of a contrast agent is clinically attractive. The T1-mapping as a single criterion demonstrated around 88% sensitivity, specificity in differentiating viable from nonviable myocardium in chronic MI. Our results were similar to the study by Ferreira et al looking at the accuracy of T1-mapping in delineating the extent and patterns of acute myocarditis.(201) It may be possible in future to perform a contrast-free CMR protocol using cine and T1-mapping for the assessment of TEI.

Viability assessment is a common indication for CMR not only in chronic IHD but also in acute MI. The latest ESC guidelines on management of STEMI recommend viability assessment in an acute setting in selected cases (including in multivessel disease). (8)

In addition to a chronic MI group our study included an acute MI group thereby giving an opportunity to delineate the native T1 findings in acute MI patients.

The study delineated a higher accuracy of native T1 in chronic MI compared to acute for the assessment of viability. The reason behind the lower performance of native T1 in acute MI is most likely due to its pathophysiologic difference with chronic MI. Acute MI is characterised by oedema, loss of cell membrane integrity, an inflammatory response, necrosis, micro-vascular obstruction (MVO) and haemorrhage whereas chronic MI by scar tissue/fibrosis in the extracellular space. Our study showed that the mean area at risk (oedematous area) in acute MI was 31% of LV which was significantly higher than the mean infarct size (21% of LV). The myocardial oedema delineated may have impacted on the performance of T1 mapping in acute MI. T1 mapping is influenced by all of these characteristics however LGE is not (especially oedema). In acute phase even LGE based TEI have been shown to be inaccurate(202) and hence may pose a limitation as a marker of viability/functional recovery. Beek et al demonstrated that 25% of segments with 75% to 100% TEI in acute MI had functional improvement at 13 weeks. (203)

Our study was performed on 1.5T scanner but the results were comparable to the study by Kali et al (195) in which they reported the diagnostic accuracy of T1-mapping in the detection of transmural myocardial infarction in chronic MI. Our study included both acute and chronic MI, thereby helping to compare the native T1 mapping findings in the 2 groups. Our main aim was to assess the significance of segmental native T1 as a discriminator between viable and non-viable myocardium unlike the study by Kali et al where they compared the overall transmural infarction between LGE and T1 mapping using thresholding technique. The native T1 value trends in the different infarct characteristics in acute and chronic MI in our study were comparable to the case series published by Dall'Armellina et al, although the actual values were different as her study was performed on 3T and ours at 1.5T.(204) A further study on native T1 in acute MI by Dall'Armellina et al. showed a strongly positive correlation between T1 value and the LGE TEI, but they excluded segments with MVO in the analysis. (205) The aim of our study was to assess viability without the use of contrast. It is very difficult to accurately identify MVO based on the T1 mapping alone without LGE imaging. In the study by Bulluck et al the diagnostic accuracy of T1 maps to identify MVO was 79-81% (206). Hence in our study design the segmental native T1 analysis was done blinded to LGE data without excluding MVO.

Overall global native T1 showed a significant positive correlation with infarct size and LV ejection fraction. However, when the analysis was done for the acute and chronic groups the correlation was stronger in chronic compared to acute MI. The global native T1 did not correlate with LVEF in acute MI, again this is likely due to the effect of MVO or intramyocardial haemorrhage which reduces the T1 relaxation time.

Our study was performed on a 1.5T scanner, which is the most widely used machine. We have also shown a significant correlation at an individual coronary territory level. The T1 analysis was done from the T1 maps which were available immediately on the scanner console with no need for further post-processing. Apical slices were not excluded from analysis unlike other similar studies on T1 mapping due to the potential for partial volume artefact. (189) Similar studies have often eliminated lateral wall infarcts due to off-resonance artefact, but this is less relevant at 1.5T compared to 3T. (189) Moreover, our study sample had infarcts in all the different coronary territories including the lateral wall (which we included) to reduce the selection bias and reflect real world practice, whilst most of previous studies mainly included LAD infarctions.

5.2.6 Study Limitations

This is a single centre, single vendor study with a limited sample size. However, our findings were highly statistically significant. Larger multicenter, multivendor studies are warranted to confirm this proof of concept study. TEI on LGE imaging was used as the reference standard for viability rather than functional recovery which was used in other studies. TEI <75% was used as the marker of viability in keeping with contemporary clinical practice. The acute and chronic MI cohorts were completely separate in our study unlike other studies. However, the study design was specifically constructed to remove any repeat measure from the same patient bias.

Peri-infarct grey-zone on LGE, which has been shown be associated with arrhythmic events, was not assessed. This may have explained the difference between acute and chronic MI.

5.2.7 Conclusions

Native T1 mapping correlates significantly with TEI thereby differentiating between normal, infarcted viable, and infarcted non-viable myocardium with distinctive T1 profiles in both chronic and acute MI. Native T1 mapping performed better in chronic MI compared to acute due to the absence of myocardial oedema and microvascular obstruction. T1 mapping holds promise for viability assessment without the need for gadolinium contrast agents.

The work presented in this chapter has been published in the following research article. I was the first author in the paper with Dr Chiara Bucciarelli-Ducci as the senior author: (207)

Dastidar AG, Harries I, Pontecorboli G et al. Native T1 mapping to detect extent of acute and chronic myocardial infarction: comparison with late gadolinium enhancement technique. Int J Cardiovasc Imaging 2018 Oct (epub ahead of print)

I presented the abstract of the work at **British Society of Cardiovascular Imaging Conference 2017** and won the **Best Poster Abstract Award**.

6 Conclusion

CMR is a well-established, comprehensive, increasingly used non-invasive imaging modality for the assessment of patients with IHD, both in the acute and chronic setting. CMR can assess cardiac anatomy, function, myocardial perfusion and tissue characterization, without exposure to ionising radiation and in <1h scan time. Its use in IHD is supported by robust and rapidly expanding evidence. The real challenge is to delineate how CMR can improve patient management and improve clinical outcomes in a cost-effective manner.

Key findings of this thesis are:

- In a large cohort of MINOCA, CMR (median 37days from presentation) established a diagnosis in almost 3/4 of cases, the most common diagnoses being myocarditis and MI, followed by cardiomyopathy.
- The diagnostic value of CMR improved significantly when carried out within 2 weeks from presentation.
- CMR made a significant additive clinical impact on management and/or diagnosis in 66% of patients, with LGE being the best independent predictor of impact. Moreover, the clinical impact of CMR improved significantly when carried out within 2 weeks from presentation.
- Among the conventional risk factors and CMR characteristics, ST-segment elevation on presentation ECG and CMR diagnosis of cardiomyopathy were independent predictors of mortality in MINOCA. Combined analysis of CMR diagnosis and ECG at presentation may allow robust stratification of patient outcomes.

- Via non-invasive advanced CMR relaxometry technique our study demonstrated that in STEMI the remote myocardium is also affected when compared to normal healthy myocardium. The native T1 in remote myocardium is an independent associate of MVO.
- Native T1 mapping correlates significantly with TEI thereby differentiating between normal, infarcted viable, and infarcted non-viable myocardium with distinctive T1 profiles in both chronic and acute MI. Native T1 mapping performed better in chronic MI compared to acute due to the absence of myocardial oedema and microvascular obstruction. T1 mapping holds promise for viability assessment without the need for gadolinium contrast agents.

7 Future direction

The studies in the thesis have contributed in the field of CMR. But further work is needed.

7.1 *In MINOCA*

- It has been demonstrated that CMR done early can identify the underlying cause for presentation however specific diagnosis based tailored therapy remains unknown
- Cardiomyopathy group in MINOCA had the worst outcome. A large randomized MINOCA study is warranted with study design similar to MR-INFORM(208) to establish the potential prognostic benefit of a CMR guided MINOCA treatment strategy
- 1/4th of the MINOCA population in the study had myocardial infarction due to embolic/spontaneous recanalization/sudden coronary artery dissection. Large scale intravascular coronary imaging guided study is warranted to delineate the potential role

7.2 *In STEMI*

- It has been demonstrated that there is widespread injury in STEMI via non contrast advanced relaxometry techniques (T1 and T2 mapping) and its association with adverse factor like MVO. However large randomized studies are warranted to delineate the clinical importance of these findings by using it as a surrogate marker.
- It has been shown that viability can be assessed by native T1mapping with the need for gadolinium contrast. However, the diagnostic accuracy was inferior compared to chronic. Advancement in the technique by enhancing

the sequence is required to improve the diagnostic accuracy for assessment of viability in acute myocardial infarction

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Appendix I

List of Publications

- **Dastidar AG, Baritussio A, De Garate E et al. Prognostic role of cardiac MRI and conventional risk factors in Myocardial Infarction with non-obstructed coronary arteries. JACC Cardiovasc Imaging 2019 Feb (epub ahead of print)**
- **Dastidar AG, Harries I, Pontecorboli G et al. Native T1 mapping to detect extent of acute and chronic myocardial infarction: comparison with late gadolinium enhancement technique. Int J Cardiovasc Imaging 2018 Oct (epub ahead of print)**
- **Hirt L, Kandan R, Rahbi H, Dastidar AG et al. Three factors combined predict futility of emergency coronary angiography in out of hospital cardiac arrest. J Am Coll Cardiol 2018 Oct;72(14):1753-1755**
- **Rodrigues JC, Erdei T, Dastidar AG et al. Left ventricular extracellular volume fraction and atrioventricular interaction in hypertension. Eur Radiol 2018 Sep (epub ahead of print)**
- **Rodrigues JC, Amadu AM, Dastidar AG et al. Nocturnal dipping status and left ventricular hypertrophy: a cardiac magnetic resonance study. J Clin Hypertens (Greenwich). 2018 Apr;20(4):784-793**
- **Dastidar AG, Rodrigues JCL, Johnson T et al. Myocardial Infarction with non-obstructed coronary artery: Impact of CMR early after presentation. JACC Cardiovasc Imaging 2017 Oct;10:1204-1206**
- **Dastidar AG, Baritussio A, Frontera A et al. Diagnostic Yield of Cardiovascular Magnetic Resonance in Young-Middle Aged Patients with High-Grade Atrio-Ventricular Block. Int J Cardiol 2017 Oct; 244:335-339**
- **Baritussio A, Zorzi A, Dastidar AG et al. Out of Hospital Cardiac Arrest Survivors with Inconclusive Coronary Angiogram: Impact of Cardiovascular Magnetic Resonance on Clinical Management and Decision Making. Resuscitation 2017 Jul; 116:91-97**

- Rodrigues JC, Rohan S, **Dastidar AG** et al. **Cardiac Magnetic Resonance Imaging provides new insight into hypertensive heart disease – a reply.** *J Clin Hypertens* (Greenwich). 2017 Mar;19(3):335-336
- Garg P, Morris P, Fazlanie AL, Vijayan S, Bancso D, **Dastidar AG** et al. **Cardiac Biomarkers of Acute Coronary Syndrome: from history to high-sensitivity troponin.** *Intern Emerg Med* 2017 Mar;12(2):147-155
- Rodrigues JC, Amadu AM, **Dastidar AG** et al. **Prevalence and predictors of asymmetric hypertensive heart disease: insights from cardiac and aortic function with cardiovascular magnetic resonance.** *Eur Heart J Cardiovasc Imaging* 2016 Dec;17(12):1405-1413
- Rodrigues JC, Rohan S, **Dastidar AG** et al. **The Relationship Between Left Ventricular Wall Thickness, Myocardial Shortening, and Ejection Fraction in Hypertensive Heart Disease: Insights From Cardiac Magnetic Resonance Imaging.** *J Clin Hypertens* (Greenwich). 2016 Nov;18(11):1119-1127
- Rodrigues JC, Amadu AM, **Dastidar AG** et al. **ECG strain pattern in hypertension is associated with myocardial cellular expansion and diffuse interstitial fibrosis: a multi-parametric cardiac magnetic resonance study.** *Eur Heart J Cardiovasc Imaging* 2017 Apr;18(4):441-450
- Rodrigues JC, Rohan S, **Dastidar AG** et al. **Hypertensive heart disease versus hypertrophic cardiomyopathy: multi-parametric cardiovascular magnetic resonance discriminators when end-diastolic wall thickness \geq 15 mm.** *Eur Radiol.* 2017 Mar;27(3):1125-1135
- Rodrigues JC, Amadu AM, **Dastidar AG** et al. **Comprehensive characterisation of hypertensive heart disease left ventricular phenotypes.** *Heart* 2016 Oct 15;102(20):1671-9
- Rodrigues JC, Lyen S, Loughborough W, Amadu AM, Baritussio A, **Dastidar AG** et al. **Extra-cardiac findings in cardiovascular magnetic resonance: what the imaging cardiologist needs to know.** *J Cardiovasc Magn Reson.* 2016 May 9;18(1):26
- **Dastidar AG**, Rodrigues JCL, Baritussio A et al. **MRI in the assessment of ischaemic heart disease.** *Heart* 2016 Feb;102(3):239-52

- **Rodrigues JC, Dastidar AG, Paton J et al. Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: An Alternative Explanation. JACC Cardiovasc Imaging. 2016 Jun;9(6):762-3**
- **Beltrami M, Ruocco G, Dastidar AG, et al. Additional value of Galectin-3 to BNP in acute heart failure patients with preserved ejection fraction. Clin Chim Acta. 2016 Jun;457:99-105**
- **Baritussio A, Dastidar AG, Bucciarelli-Ducci C. Cardiac MRI in a young man with suspected arrhythmogenic right ventricular cardiomyopathy (ARVC). Heart 2015 Nov;101(21):1703**
- **Dastidar AG, Rodrigues JCL, Baritussio A et. al. Complete revascularization in patients undergoing primary percutaneous coronary intervention for STEMI: is it really what we should be doing? J Am Coll Cardiol 2015 Jul 21;66(3):331-2**
- **Dastidar AG, Rodrigues JCL, Ahmed N et al. The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. Curr Cardiovasc Imaging Rep. 2015;8(8):28**
- **Dastidar AG, Frontera A, Palazzuoli A, et al. TakoTsubo cardiomyopathy: unravelling the malignant consequences of a benign disease with cardiac magnetic resonance. Heart Fail Rev. 2015 Jul;20(4):415-421.**
- **Rodrigues JC, McIntyre B, Dastidar AG, et al. The effect of obesity on electrocardiographic detection of hypertensive left ventricular hypertrophy: recalibration against cardiac magnetic resonance. J Hum Hypertens. 2016 Mar;30(3):197-203**
- **Palazzuoli A, Beltrami M, Gennari L, Dastidar AG, et al. The impact of infarct size on regional and global left ventricular systolic function: a cardiac magnetic resonance imaging study. Int J Cardiovasc Imaging. 2015 Jun;31(5):1037-44**

Appendix II

Prizes and distinction

- **Society for Cardiovascular Magnetic Resonance(SCMR) – Travel award 2017**
- **Best Poster Abstract Award - British Society of Cardiac Imaging Meeting 2017**
- **Finalist at the University Hospital Bristol NHS Foundation Trust Recognising Success Awards in the category - Excellence in Teaching, Learning and Research, 2017**
- **British Cardiovascular Society Travel Bursary award, 2017 and 2015**
- **British Society of Cardiac Imaging – Travel Bursary award 2016**
- **David Telling Research Fellowship Award – David Telling Charitable Trust 2016-2017**
- **Early Career Award (Clinical) - SCMR/EuroCMR Joint Scientific Sessions 2015, Nice**
- **Best Poster Diploma award - ESC Congress 2015, London**
- **Finalist – Cardiology President’s Medal Award, Royal Society of Medicine, London 2015**